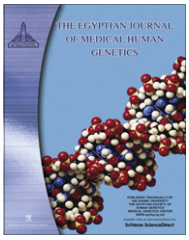
The Egyptian Journal of Medical Human Genetics (2012) **13**, 233–237

Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



CASE REPORT

Facial dysmorphism, skeletal anomalies, congenital glucoma, dysplastic nails: Mild Rubinstein-Taybi Syndrome

Rabah M. Shawky [a,*], Nermine S. Elsayed [b], Neveen S. Seifeldin [c]

[a] *Pediatric and Genetics Department, Ain-Shams University, Cairo, Egypt*
[b] *Medical Genetics Center, Ain-Shams University, Cairo, Egypt*
[c] *Dermatology, Venereology Department, Ain-Shams University, Cairo, Egypt*

Received 20 December 2011; accepted 18 January 2012
Available online 22 April 2012

KEYWORDS

Rubinstein-Taybi Syndrome;
Congenital glaucoma;
Megalocornea;
Broad halluces;
Kyphosis;
Broad thumbs;
Dysplastic nails

Abstract Rubinstein-Taybi Syndrome (RTS) is a multiple congenital anomaly syndrome characterized by mental retardation, broad thumbs and toes, short stature, growth retardation and distinctive facial features. We report an Egyptian patient, 5 months old with mild RTS. Our patient had mild mental retardation, growth retardation, microcephaly, hypertelorism, prominent peaked nose, high arched palate, mild micrognathia, low set posteriorly rotated ears, hirsutism, broad halluces, short 5th toe and dorsal kyphosis. However the antemongoloid slant and board thumbs and fingers were slightly evident. Also our patient had dysplastic toe nails and bilateral congenial glaucoma, with megalocornea and corneal haziness. Congenital glaucoma is considered a rare complication in RTS and dysplastic nails were not previously reported in RTS. High resolution karyotype was normal. Previous studies have documented considerable change in facial phenotype and skeletal changes with age. We consider our patient as having mild form of RTS and the features will be more evident as she grows older.

1. Introduction

Rubinstein-Taybi Syndrome (RTS) is a rare developmental disorder, characterized by cranio-facial dysmorphism, broad thumbs and toes as well as mental and structural deficiencies [1].

RTS has a prevalence of 1:330,000 live births [2]. In the mentally retarded institutionalized population older than 5 years of age, its frequency has been estimated at 1:300–500 [3]. This syndrome usually occurs sporadically, although it can be inherited as an autosomal dominant disorder [2,4,5].

Congenital abnormalities are quite common in RTS, however data on ophthalmological findings are rare [6,7] and congenital glaucoma is considered a rare complication in this syndrome [8].

* Corresponding author.
E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).

Peer review under responsibility of Ain Shams University.
http://dx.doi.org/10.1016/j.ejmhg.2012.03.009

ELSEVIER **Production and hosting by Elsevier**

There is considerable clinical heterogeneity in this disorder as there is much variation in the severity of the features and only few patients have all the clinical features [9].

Here we report an Egyptian infant with mild facial dysmorphism, skeletal changes, bilateral congenital glaucoma and dysplastic toe nails after taking informed consent from parents.

2. Case description

The propositus, a 5 month old female patient was the first child of consanguineous parents. The mother had a history of a previous spontaneous abortion. The patient was admitted to pediatric hospital for the treatment of pneumonia and consultation for dorsal kyphosis. The antenatal history was irrelevant with no history of preeclampsia or drug intake. There was a past history of bilateral trabeculectomy for congenital glaucoma in the patient at the age of 2 months.

On examination, skull circumference was 39.5 cm (5th–10th percentile), length 50 cm (< 3rd percentile), weight 5.5 kg (10th percentile). Anterior fontanel was widely opened (10×10 cm), posterior fontanel was 2×2 cm with opened sagittal suture. The patient had mild mental retardation, hirsutism in forehead, sides of the face and back, heavy arched eyebrows, long eyelashes, nearly rounded face with micrognathia. The patient also had hypertelorism, bilateral megalocornea with haziness, left divergent squint, depressed nasal bridge, prominent slightly peaked nose, deep groove in the philtrum, slightly protruded lower lip, high arched palate, low set posteriorly rotated ears with rudimentary lobules, low anterior and posterior hairlines and short neck (Figs. 1 and 2).

Hands showed deep creases in the palms with unilateral Sydney crease, slightly broad ends of fingers and thumbs (Figs. 3 and 4).

The feet showed broad ends of toes especially the big toe, bilateral partial syndactyly between 2nd and 3rd toes with overriding of 2nd over the 3rd and 5th over the 4th toes, short thumbs and 5th toes, with medial deviation of 4th and 5th toes. Nails were slightly dystrophic (Fig. 5).

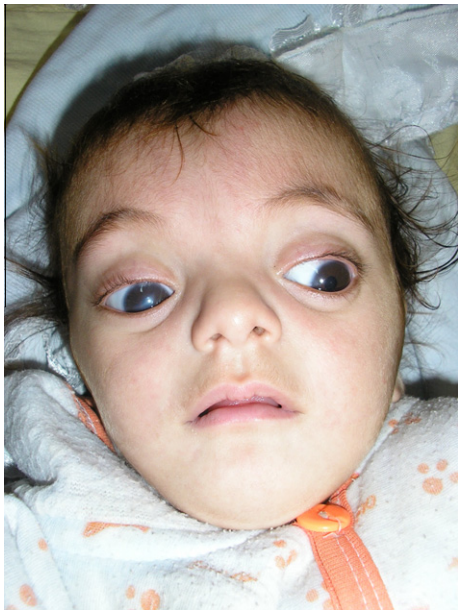


Figure 1 Slight antemongoloid slant, megalocornea with haziness and left divergent squint.

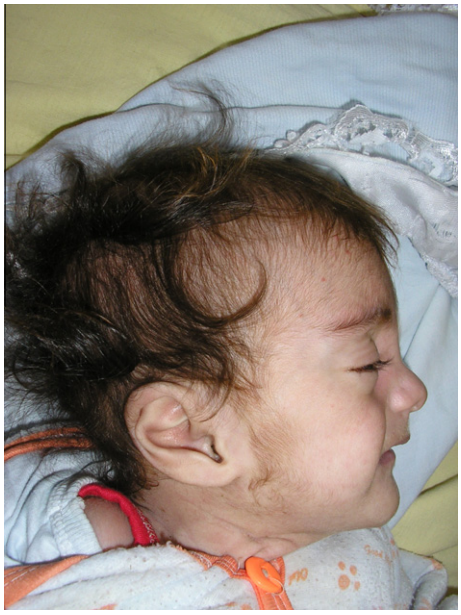


Figure 2 Low set posteriorly rotated ears, hirsutism of face, micrognathia and peaked nose.

Figure 3 Hands showed deep creases in the palms with unilateral Sydney crease.

Chest was short with protruded sternum and 2 depressions on both sides (Fig. 6). The back showed dorsal kyphosis (Fig. 7). There was clinical evidence of bronchopneumonia.

Leucocytic count demonstrated mild leucocytosis with absolute neutropenia. Echocardiography detected no abnormality. Abdominal-ultrasonography demonstrated slightly enlarged liver and spleen. Scan of the eyes and orbits demonstrated right obvious optic disc cupping. X-ray spine demonstrated mild kyphosis of dorsal spine. Audiological study was normal. Karyotype with high resolution banding was also normal.

3. Discussion

We report a 5 month old female patient with some facial and skeletal abnormalities in favor of RTS [1,2,4,5]. These features included postnatal growth retardation and head circumference

Figure 4 Slightly broad fingers and thumb.

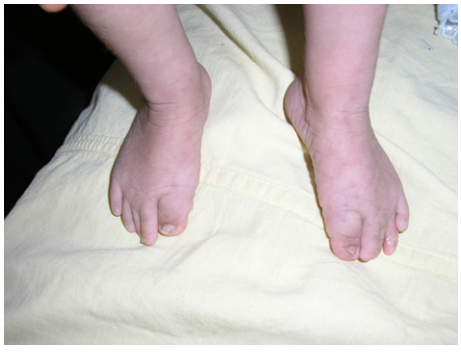


Figure 5 Broad ends of thumbs and toes, short 5th toe and dysplastic nails.

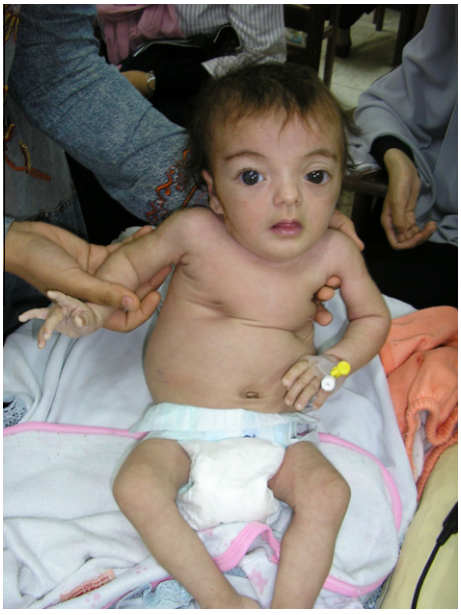


Figure 6 Short chest, protruded sternum with two depressions on both sides.

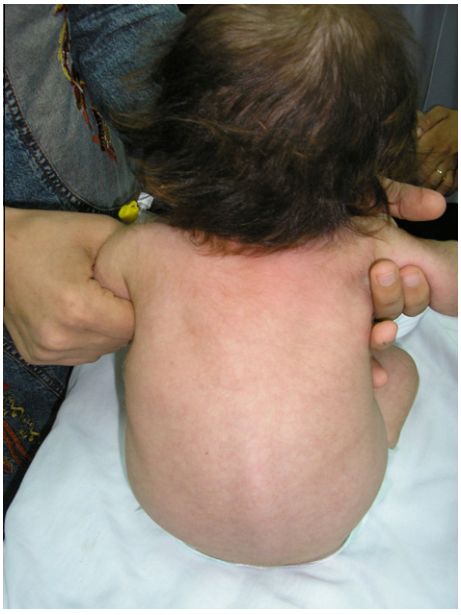


Figure 7 Dorsal kyphosis.

below the 10th percentile, mild mental retardation hypertelorism, long eyelashes, prominent and slightly peaked nose with slightly long columella, low set posteriorly rotated ears with dysplastic helices, high arched palate, hirsutism short broad big toes and short 5th toes.

However some characteristic features reported in RTS were slightly evident mainly antemongoloid slant and skeletal changes in the hands. Also the mentality was mildly affected in our patient. In RTS intellectual deficit is usually so severe that they are confined to mental institutions [8].

Previous studies have documented considerable change in facial phenotype with time [9]. In the neonate this syndrome can be confused with the de Lange syndrome, trisomy 13, Apert syndrome and Pfeiffer syndrome [8] and the typical facial phenotype may not be obvious until late childhood [10]. Also some patients exhibited milder skeletal findings on the hands and feet than those typically observed in patients with RTS [11].

Our patient had hirsutism of face and back. Dermatologic features are frequently reported in RTS patients including hirsuitism, capillary malformations in approximately 50 percent of patients and higher incidence of keloid and hypertrophic scars [12], pilomatricomas [13] ingrown toe nails, paronychia [14] and dermatoglyphics abnormalities [15]. However our patient had dystrophic toe nails in both feet, which was not reported previously.

In RTS there may be systemic involvement of a multiple organ system. Twenty-four to twenty-eight percent of these children have cardiac abnormalities including atrial and ventricular septal defects, patent ductus arteriosus and bicuspid aortic valve [16]. In our patient no cardiac abnormality was detected.

There were also case reports of children with RTS with an element of immune deficiency, contributing to frequent significant infection [17]. Our patient was admitted to the hospital for treatment of severe bronchopneumonia and he had received two doses of polio and DPT vaccination which were followed by high fever. There were also reports of five percent complication rate for immunization as fever, irritability and/or vomiting [5]. Our patient demonstrated slightly enlarged liver and spleen and slight leucocytosis with mild absolute neutropenia. Torres observed splenomegaly in their patient at 21 years of age and a detailed immunological analysis of the patient was performed where persistent mild to moderate leucocytosis was observed despite the absence of clinical signs of infection [18]. Our patient suffered from pneumonia and this can explain leucocytosis. As RTS patients have an increased risk of hematological malignancies appropriate laboratory testing and hematological follow up is warranted [19].

Children with RTS suffer from seizures in 27–28% and abnormal EEG findings in 57–66% [1] and there was increased risk of neural tumors [20], and spinal cord malformations [21] which were not reported in our patient.

There have been also case reports of hyper or hypoglycemia [1], gastroesophageal reflux which causes nutritional problems [2], hirshsprung disease, strictures of the esophagus [22], renal anomalies in 52 percent of patients [2], incomplete or delayed descent of testes in 78–100% of patients [5]. Dental anomalies were also reported in 67 percent of patients including crowding and malpositioned teeth [1]. Our patient was still 5 months old and he had no gastro-intestinal anomalies.

Skeletal abnormalities observed in RTS patients include small and short stature, retarded osseous maturation, and hypoplastic maxilla with a narrow palate [8]. Our patient had all these characteristic abnormalities as well as dorsal kyphosis which was also reported in one of his paternal relatives. Apart from hypotonia, no neurological symptoms were reported in our patient. Rubinstein [1] reported that children with RTS could have congenital or acquired scoliosis, however it appeared very early in our patient and Tatora et al., [23] believed that it is due to neuromuscular abnormalities.

Our patient also suffered from bilateral congenital glaucoma which was operated upon shortly after birth, together with bilateral haziness of the megalocornea and right optic disc cupping. Ocular and adenexal abnormalities are quite common in RTS. Antemongloid slant of palpebral fissures is seen in 93% of patients, epicanthic folds in 54%, congenital obstruction of lacrimal ducts in 19%, ptosis and strabismus especially exotropia in 61% and severe ametropia especially high grade myopia in 76%. Macrocornea, microphthalmos, colobomas of the iris and of optic nerve head, congenital cataract and optic nerve atrophy have also been described, as has congenital glaucoma, although this is a rare complication [6,8,24].

Although the parents of our patient were consanguineous, we believe that our patient is a sporadic case as there was no family history of an affected relative. RTS usually occurs sporadically, although it can be inherited as an autosomal dominant disorder (Wiley, 2003) [16]. RTS typically occurs as a de novo mutation in a family and the parents are not affected. The empiric recurrence risk for siblings is approximately 0.1%. Although individuals with RTS rarely reproduce, the theoretical risk for the offspring is 50% [4].

The cause of RTS is still unclear. Ten percent of patients with RTS have a microdeletion at 16p13.3 region, 40–50% carry a mutation of the CREBBP gene and another 3% have a mutation in the EP300 gene. Both genes are highly homologous and play important roles as global transcriptional coactivators and functions as a potent histone acetyl transferase, both of which are essential for normal development [25]. In the remaining patients with clinically suspected RTS no mutation could be detected.

Wieczorek, [24] described 2 patients with the characteristic facial RTS, broad thumbs and big toes, mild mental retardation, formation of keloids and glaucoma, but without postnatal growth retardation or microcephaly. In addition they have both congenital camptodactyly of 3rd and 4th fingers which had not been reported previously. Of these two patients, one was seen with a mutation in CREBBP gene and the other without a mutation in this gene or in the EP300 gene and without a chromosomal imbalance on high resolution array. The author suggested that these 2 patients represent a clinical subtype of RTS. However there are reports of patients with deletion of exon 3–8 or mutations of the EP300 gene who had mild skeletal phenotype [11,26] and the forefoot was broad and the 5th toe was shorter than normal [26] similar to our patient. Clinically the difference between patients with or without deletion is minimal except for microcephaly. Band 16p3.3 seems to be an important locus for mental retardation in patients with correct diagnosis of RTS [27]. Also Roelfsema, et al. [25], examined 92 patients with RTS, among them one patient had a small chin and another patient showed a very mild downward-slanting of the palpebral fissures and none had the grimacing smile. One patient had remarkably short first metatarsal bones giving rise to very proximally placed halluces which is similar to those of our patient.

Since mental retardation is considered a part of the syndrome an autopsy case of RTS demonstrated a moderate degree of cerebral cortical and callosal hypoplasia and diffusely disturbed neuronal anoxic changes possibly associated with cardio- pulmonary insufficiency [28].

Prenatal testing for risk pregnancies is possible if the disease causing CREBBP mutation or deletion in a family is known [25].

To conclude, there is considerable clinical variability and much variation in severity in patients with RTS which can be explained by genetic heterogeneity and the diagnosis must expand to include patients without broad thumbs or halluces or antemongoloid slant.

References

[1] Rubinstein JH. Broad thumbs-hallux (Rubinstein-Taybi) syndrome 1957–1988. Am J Med Genet Suppl 1990;6:3–16.

[2] Hennekam RCM, Stevens CA, Van de Kamp JJP. Etiology and recurrence risk in Rubinstein-Taybi syndrome. Am J Med Genet Suppl 1990;6:56–64.

[3] McKusick VA. In: McKusick VA, editor. Mendelian inheritance in man: Catalogs of autosomal dominant, autosomal recessive and X-linked phenotypes. Baltimore: John Hopkins University Press; 1986. p. 1239.

[4] Leuridan Cavalcante Torres, Maria de Lourdes Lopes Chauffaille, Thomaz Pileggi Delboni, Thelma Suely Okay, Magda Carneiro-Sampaio, Sofia Sugayama. Rubinstein-Taybi Syndrome: A female patient with a denovo reciprocal translocation t(2;16)(q36.3; p13.3) and Dysgranu-lopoiesis. Clinics (Sao Paulo) 2010, 65(1): 107–9.

[5] Stevens CA, Carey JC, Blackburn BL. Rubinstein-Taybi syndrome: a natural history study. Am J Med Genet Suppl 1990;6:30–2.
[6] Brei TJ, Burke MJ, Rubinistein JH. Glucoma and findings simulating glaucoma in Rubinstein-Taybi syndrome. J Pediatr Ophthalmol Strabismus 1995;32:248–52.
[7] VanGenderen MM, Kinds Geert, Riemslag FCC, Hennekam RC. Ocular features in Rubinstein-Taybi syndrome: investigation of 24 patients and review of the literature. Br J Ophthalmol 2000;84:1177–84.
[8] O'Neil DW, Canada RT, Clark MV, Lowe JW. Rubinstein-Taybi syndrome: Case report. Pediatr Dentistry 1989;11(2):158–60.
[9] Allanson JE, Hennekam RCM. Rubinstein-Taybi syndrome: Objective evaluation of craniofacial structure. Am J Med Genet 1997;71(4):414–9.
[10] Allanson JE. Rubinstein-Taybi syndrome: The changing face. Am J Med Genet Suppl 1990;37(S6):38–41.
[11] Bartholidi D, Roelfsema JH, Papadia F, Breuning MH, Niedrist D, Hennekam RC, et al.. Genetic heterogeneity in Rubinstein-Taybi syndrome: delineation of the phenotype of the first patients carring mutations in EP300. J Med Genet 2007;44(5):327–33.
[12] Siraganrian PA, Rubinistein JH, Miller RW. Keloids and neoplasms in the Rubinstein-Taybi syndrome. Med Pediat Oncol 1989;17:485–9.
[13] Dalal AB, Phadke SR. Morphologic analysis of face in dysmorphology. Comput Methods Programs Biomed 2007;85(2):165–72.
[14] Masuno M, Imaizumi K, Ishii T, Kuroki Y, Baba N, Tanaka Y. Pilomatrixomas in Rubinistein-Taybi syndrome. Am J Med Genet 1998;77:81–4.
[15] Cambiaghi S, Emacora E, Brusasco A, Canzi L, Caputo R. Multiple pilomatricomas in Rubinstein-Taybi syndrome: a case report. 1994;11(1):21–5.
[16] Wiley S, Swayne S, Rubinstein JH, Lanphear NE, Stevens CA. Rubinstein-Taybi syndrome medical guidelines. Am J Med Genet 2003;119A:101–3.
[17] Villela A, Bialostocky D, Lori E, Meyerson M, Hostoffer R. Rubinstein-Taybi syndrome with humoral and cellular defects. A case report. Arch Dis Child 2000;83:360–1.
[18] Torres LC, Avaliação da imunocompetência de portadores da síndrome de Rubinstein-taybi. (Tese de Doutorado). Universidade de Sao Paulo, Brasil. 2008.
[19] Miller RW, Rubinistein J. Tumors in Rubinstein-Taybi syndrome. Am J Med Genet 1995;56:112–5.
[20] Burton B, Kumar G, Bradford R. Ganular cell tumour of the spinal cord with Rubinstein-Taybi syndrome. Br J Neurosurg 1996;3:257–9.
[21] Rosenbaum K, Johnson D, Fitz C, McCullough D- Tethered cord in Rubinstein-Taybi syndrome: Am J Hum Genet Supplement, 1990, 47:A75.
[22] Scott A, Proops D, Kunickt. Post-cricoid web associated with Rubinstein-Taybi syndrome. J Laryng Otol 2000;114:637–8.
[23] Tatora Y, Kawakami N, Tsuji T, Miyasaka K, Ohara T, Nohara A. Rubinstein-Taybi syndrome with scoliosis. Scoliosis 2011;6:21–2.
[24] Wieczorek D, Bartsch O, Lechno S, Kohihase J, Peters DJM, Dauwerse H, et al.. Two adults with Rubinstein-Taybi syndrome with mild mental retardation, glucoma, normal growth and skull circumference and camptodactyly of a third fingers. Am J Med Genet 2009;149A(12):2849–54.
[25] Roelfsema JH, White SJ, Ariyurek Y, Bartholidi D, Niedrish D, Papadia F, et al.. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both CBP and EP300 genes cause disease. Am J Hum Genet 2005;76:572–80.
[26] Foley P, Bunyan D, Stratton J, Dillon M, Lynch SA. Further case of Rubinstein-Taybi syndrome due to a deletion EP300. Am J Me Genet 2009;149A:997–1000.
[27] Stef M, Simon D, Mardirossian B, Delrue MA, Burgelin I, Hubert C, et al.. Spectrum of CREBBP gene dosage anomalies in Rubinstein-Taybi syndrome patients. Eur J Hum Genet 2007;15(8):843–7.
[28] Fukunoga N, Suda S, Ebihara Y, Laovoravit N, Laovoravit M. Rubinstein-Taybi syndrome - a case report. Patholo Int 1969;19(4):501–10.