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.

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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].
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 dystrophic 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).

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...
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 hirsutism, capillary malformations in approximately 50 percent of patients and higher incidence of keloid and hypertrophic scars [12], pilomatrixomas [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 signif-
ificant infection [17]. Our patient was admitted to the hospital
for treatment of severe bronchopneumonia and he had re-
ceived two doses of polio and DPT vaccination which were fol-
lowed 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 li-
ver and spleen and slight leucocytosis with mild absolute neu-
tropenia. 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 leuc-
ocytosis 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], hirschsprung 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 abnormalities.

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 rela-
tives. 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] be-
lieved that it is due to neuromuscular abnormalities.

Our patient also suffered from bilateral congenital glau-
coma which was operated upon shortly after birth, together
with bilateral hazziness of the megalocornea and right optic disc
cupping. Ocular and adnexal abnormalities are quite common
in RTS. Antemongold slant of palpebral fissures is seen in
93% of patients, epicanthic folds in 54%, congenital obstruc-
tion 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 op-
tic 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 spo-
radically, although it can be inherited as an autosomal domi-
nant disorder (Wiley, 2003) [16]. RTS typically occurs as a
denovo mutation in a family and the parents are not affected.
The empiric recurrence risk for sibs is approximately 0.1%.
Although individuals with RTS rarely reproduce, the theore-
tical 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% car-
ry a mutation of the CREBBP gene and another 3% have a
mutation in the EP300 gene. Both genes are highly homolo-
gous and play important roles as global transcriptional coacti-
vators 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 muta-
tion could be detected.

Wieczorek, [24] described 2 patients with the characteristic
facial RTS, broad thumbs and big toes, mild mental retarda-
tion, formation of keloids and glaucoma, but without postna-
tal 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 with-
out 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 skel-
etal phenotype [11,26] and the forefoot was broad and the 5th
toe was shorter than normal [26] similar to our patient. Clin-
cally 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 syn-
drome an autopsy case of RTS demonstrated a moderate de-
gree 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 ex-
and to include patients without broad thumbs or halluces
or antemongoloid slant.

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