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Rubistein-Taybi syndrome. Review of 732 cases and analysis of the typical traits

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Abstract. – **In 1963 Rubinstein and Taybi described a new syndrome characterized by broad thumbs and toes, facial abnormalities and mental retardation. The syndrome can be observed in the neonatal period by typical thumbs, halluces and facial abnormalities. The prevalence in the general population is unknown, however the disorder is not rare and is present in about 1:600 patients in mental retardation clinics. At the present time there is no definite inheritance pattern and recurrence is very unlikely. 18 different chromosomal anomalies have been identified in some patients with this syndrome. In this paper we identify a typical case and review the symptoms and signs of the RT syndrome and meta-analyze 732 cases.**

Key Words:

Rubinstein-Taybi syndrome, Chromosome 16 p13.3, Mental retardation, CBP gene.

Introduction

In 1963 Rubinstein and Taybi described a new syndrome characterised by broad thumbs and toes, facial abnormalities and mental retardation. Rubinstein-Taybi syndrome (RTS) represents one of the classical recurrent-pattern multiple congenital anomaly syndromes. The first observation dates from 1957. In this year Rubinstein evaluated a 3,5 year-old girl with unusual facial appearances and broad thumbs and great toes[29]. However in the same year Michail et al[24] from Athens published a case report in a French orthopedic journal. Since then more than 700 cases have been reported world-wide. The prevalence of RTS in the general population is unknown, perhaps it is 1/300.000. Reports of frequencies for instituzionalized populations in the 1960s varied from 1/267 in Cincinnati, 1/300 in Canada, 1/500 in England to 1/720 in California[29].

The cause of RTS is still unclear. As regards its inheritance, a comparison between epidemiological data from Netherlands (45 cases) and USA (50 cases) with data from patients reported in the literature (407 cases) shows that empirical recurrence risk figure for sibs is 0,1%; the recurrence risk for offspring of affected individuals could be as high as 50%[17].

In this paper we discuss all the recent pertinent data and meta-analyze the clinical manifestations as yet reported to characterize the index RTS case.

Genetics

Up to few years ago the RTS is listed as an autosomal recessive trait, but subsequent studies do not confirm this suggestion. More recently an autosomal dominant inheritance has been found in RTS-like, according to some family studies[6]. Moreover in 1989 Hennekham reported a case of dominant transmission in a mother and son[12]. A microdeletion of chromosomal material at 16p 13.3 has been found in some patients with the disorder, but no such deletion can be identified in the majority of affected individuals[21]. In a recent study by Hennekham et al 19 patients with RTS underwent a cytogenetic investigation with FISH[13]. It was found a deletion at chromosome 16p 13.3 and molecular studies showed a copy of chromosome 16 from each parent in all 19 patients. Therefore a small deletion at 16p 13.3 may be found in some patient with RTS. More recently other two studies confirm the presence of a deletion at chromosome 16p 13.3 in patients with RTS[23,38].

Cytogenetic studies of a patient with typical RTS reported by Imaizumi and Kuroki[17] showed an apparently chromosomal rearrangements

with breakpoint at 16 p13.3 without visible deletion, who the karyotype was: 46, XX, t(2;16) (p13.3;p13.3). Her parents had normal chromosome[17].

Another apparently balanced de novo reciprocal translocation, t(7;16) (q34;p13.3) was detected in an affected boy[34]. With these information Hennekham documents in 25% of patients with RTS a submicroscopic deletion at the chromosome 16 in the region p13.3 by FISH. These results confirm that the locus of the gene for the RTS may be situated at 16 p13.3[21]. More recently Petrij et al reported that these breakpoints are restricted to a region that contains the gene for the human CREB binding protein (CBP)[27]. He suggested that RTS results from chromosomal rearrangements of chromosome 16p, but also from point mutation in the CBP gene[27].

The mutations in the CBP gene are responsible for RTS as well as the t(8;16)-associated acute myeloid leukemia[10].

One clear-cut case parent-to-child transmission has been reported, furthermore a mother and daughter, both of whom appear to be affected with RTS strongly suggest either autosomal or X-linked dominant transmission[21]. The paucity of previous cases of parent-to-child transmission may be related to either decreased fertility or decreased fitness in affected individuals[21]. Therefore the most likely explanation is an autosomal dominant mutation, either as submicroscopic chromosome deletion or duplication, or point mutation[14].

In addition a two month-old girl was diagnosed as a case of RTS on a typical facial dysmorphism, broad and duplicated distal phalanges of thumbs and halluces, growth retardation and psychomotor development delay[18]. Chromosomal analysis showed a de novo pericentric inversion of one chromosome 16. The karyotype is: 46, XX, inv[16] (p13.3; q13)[18]. This association confirms assignment of a locus for RTS gene to 16 p13.3, as two others translocation involving the same breakpoint have already been reported. In addition there are several patients with chromosome anomalies of doubtful characterization. Finally two individuals with trisomy were previously identified as having RTS. A stillborn anencephalic fetus with 46 XY, del 17q22 cannot be included, because the typical facial appearance was absent[35].

However clinically the difference between patients with or without microdeletion are minimal[12]; but incidence of microcephaly, angulation of thumbs and halluces and duplication of halluces is different. Band 16 p13.3 seems to be an important locus for mental retardation[18]. The function of gene situated in this region could be lost for minimal loss of chromosomal material resulting from translocation[17]. Therefore in RTS this deletion is very significant in malformation. Most cases are sporadic and no cytogenetic anomalies are found. Cytogenetically undedectable deletion, point mutation, mosaicism, heterogeneity or point mutations in CBP gene or phenocopy by a nongenetic cause are the most likely explanations for absence chromosomal anomalies in some of affected patients[17]. Studies of twins have been inconclusive[9-11,13-26,28].

In Table I we gather the chromosomal anomalies that we found up to now.

Materials and Methods

We considered 732 patients as study group from world literature. We identify the typical cases and review the symptom and signs of this syndrome by meta-analysis of 17 papers.

The diagnosis of these patients is the Rubinstein-Taybi syndrome; 571 cases are reported in a study by Rubinstein[29]; they come from 40 countries. Additionally 45 patients live in Netherlands[14], 50 in USA[15], 4 in France[19] and 11 in Canada[26].

Bellini and Boniolo[3] report further 11 cases with age-range 1-13 years. One patient[4] presents intracranial angioblastic meningioma with RTS and another patient shows RTS associated with Dandy-Walker malformation[22].

Battaglia and Ferrari[1] report 6 cases of this syndrome and they investigate particularly the cognitive and psychological profiles of these patients.

Robinson and Stewart[28] report a case of male twins from Kentucky and Ghanem and Dawood[9] a case of monozygotic twin sister from Qatar.

We found 5 articles[13,17,18,21,36], reporting 29 cases and studying the genetic causes of RTS.

We gathered all symptoms and signs of these patients in Tables II-IX and we looked

Table I.

Kariotype identified	Classification	Reference
46, XX/47+der (20) (qter 13.3 p11.2)	Mosaic trisomy	(37)
47, XX	Trisomy X	
46, XY/47, XY+F/47, XY+G, del (2p)	Mosaic trisomy	(2)
46, XX, ? var (C)	Variant	(7)
46, XY, del (?10p or ?12p)	Deletion	(20)
46, XY 16qh+	Polymorphism	(8)
46, XXn Dph+	Polymorphism	(30)
Translocation G-group chromosome with 13-15 chromosome	Translocation	(31)
47, XX+G or 47, XX+del (14q)	Trisomy	(32)
Del 1q43; variant 16 or 17	Del variant	(35)
t (14q1-7p13 or 7q3)	Translocation	(38)
46, XX? var (c)	Variant	(11)
46, XX, Y qh+	Polymorphism	
46, XX, del (1) (q?24)	Deletion	
46, XY, 17s+16qh+	Polymorphism	
46, XY 16qh-	Polymorphism	(16)
46, XX, 9qh+	Polymorphism	
46, XX, 9qh+	Polymorphism	
46, XY, 16qh+	Polymorphism	(25)

at the principal manifestations of this rare syndrome. Up to now no pathognomic criteria exists for the RTS diagnosis.

Results

Broad thumbs and halluces associated with facial appearance are considered as essential finding of the RTS.

In the 732 patients we found a lot of clinical traits, about 80. In the medical history these subjects often show polyhydramnios, birth weight 2500 g or less, neonatal distress, severe feeding abnormalities and respiratory infections (Table II). In the older age there were stature under 50th percentile (or 5th percentile), bone age under 50th percentile, allergy and chronic constipation (Table III).

However the most evident symptoms are the thumbs and first toes with broad terminal phalanges (99%) and often the other fingers with broad terminal phalanges too (74%).

Table IV shows the most common abnormalities of thumbs and limbs. The trunk presents many anomalies too, as spina bifida, scoliosis, kyphosis, lordosis, hypotonia, lax ligaments and above all stiff gait (83,8%).

The typical face may be evident in the first few years of life or may not be evident until childhood. The face appears with beaked nose, broad nasal bridge, nasal septum alae, palate anomaly, grimacing smile, palpebral fissures, antimongoloid slant, and apparent hypertelorism. The ears are often abnormal in position, rotation, size or shape(75.7%) (Table V). The ophthalmologic problems are above all strabismus (60.7%) and refractive errors (50%) but often these patients present coloboma, ptosis, cataract and nasolacrimal duct obstruction.

In adults were noted head circumference under 50th percentile (95%) or microcephaly (87%) (Table V).

Hirsutism and capillary hemangiomas are frequent (Table VI). Kidney anomalies or disease are equally frequent (Table VII). In the males we found testes anomalies in 82% of the cases and cryptorchidism in 30 cases (Table VIII).

Heart and cardiovascular manifestations are not very common; cardiac defects were found in 136 patients and heart murmur in 150 patients (Table VIII).

Mental, motor, language and social retardation is one of the most common symptoms in RTS; it is present in 98.5% of the patients and IQ is often under 50 (Table IX). In Table X we report psychomotor development in

Table II.

Typical clinical manifestations in 732 RTS cases	
Birth:	
Severe feeding in infancy	76.3%
Neonatal distress or respiratory infections in infancy	75.6%
Older age:	
Stature under 50th percentile	92.7%
Stature under 5th percentile	77.5%
Bone age under 50th percentile	73.6%
Obstipation	59.4%
Face	
Head circumference under 50th percentile	95.0%
Narrow palate or palate highly in appearance	93.0%
Palpebral fissures antimongoloid sllant	90.0%
Beaked nose	87.0%
Microcephaly	87.0%
Hypertelorism apparent	83.0%
Nasal bridge broas	81.8%
Nasal septum alae	80.0%
Smile grimacing	76.0%
Abnormal ears in position, size rotation or shape	75.7%
Deviated nasal septum	71.7%
Micro/retrognathia	70.0%
Eyebrows: heavy or highly arched	69.6%
Epicanthi	68.0%
Dental anomalies	67.4%
Strabismus	
Small mouth	59.3%
Long eyelashes	57.8%
Trunk:	
Gait stiff	83.8%
Vertebral anomalies	75.3%
Hypotonia, lax ligaments and hyperextensible joints	71.6%
Pelvic anomalies	60.7%
Sternal or rib anomalies	57.3%
Limbs:	
Thumbs and first toes with broad terminal phalonges	99.0%
Other fingers with broas terminal phalanges	74.0%
Fifth finger clinodactyly	50.3%
Other anomalies:	
Motor, mental, language and social retard	98.5%
Testes: incomplete or delayed descent	82.0%
Hirsutism	76.0%
I.Q. under 50	73.0%
Cryotorchidism	67.0%
EEG abnormalities	57.6%
Capillary hemangioma	56.6%
Kidney anomalies or disease	50.7%

Table III.

Main symptoms and signs in RTS patients	
Birth:	
Severe feeding in infancy	76.3%
Neonatal distress or respiratory infections in infancy	75.6%
Polyhydramnios	22.6%
Birth weight 2,500 gr or less and birth weight below 3rd percentile	18.8%
Older age:	
Stature under 50th percentile	92.7%
Stature under 5th percentile	77.5%
Bone age under 50th percentile	73.6%
Obstipation	59.4%
Allergy	38.0%

children with RTS[31]: it clearly shows a remarkable retard of these affected children, according with our studies.

From these information we meta-analyze the most common symptoms and signs of this syndrome and identify the typical clinical manifestations in these patients (Table II).

Table IV.

Main symptoms and signs in RTS patients	
Limbs:	
Thumbs and 1st toes wiwth broad terminal phalanges	99.0%
Other fingers with broad terminal phalanges	74.0%
Fifth finger clinodactyly	50.3%
Overlapping toes	45.6%
Thumbs and 1st toes angulation with abnormal shape proximal phalanges or 1st metatarsal	33.0%
Trunk:	
Stiff gait	83.8%
Vertebral anomalies as spina bifida, kyphosis, lordosis or scoliosis	75.3%
Hypotonia, lax ligamentes and hyperextensible joints	71.6%
Pelvic anomalies	60,7%
Sternal or rib anomalies	57.3%
Obesity	31.0%

Table V.

Main symptoms and signs in RTS patients	
Face-head:	
Head circumference under 50th percentile	95.0 %
Narrow palate, palate highly arched in appearance	93.0 %
Palpebral fissures, antimogoloid slant	90.0 %
Microcephaly	87.0 %
Beaked nose	87.0 %
Apparent hypertelorism	83.0 %
Nasal bridge broad	81.8 %
Nasal septum alae	80.0 %
Smile grimacing	76.0 %
Deviated nasal septum	71.7 %
Micro/Retrognathia	70.0 %
Eye-brows: heavy or highly arched	69.6 %
Epicanthi	68.0 %
Dental anomalies	67.4 %
Strabismus	60.7 %
Small mouth	59.3 %
Long eyelashed	57.8 %
Frontal bossing or forehead prominence	57.0 %
Large anterior fontanel or late in closing	53.0 %
Refractive errors	50.0 %
Foramen magnum large	50.0 %
Nasolacrimal duct obstruction	38.0 %
Ptosis	32.0 %

Table VI.

Main symptoms and signs in RTS patients	
Skin:	
Hirsutism	76.0 %
Capillary hemangiomas	56.6 %
Deep plantar between 1st and 2nd toes	56.0 %
Keloid formation	23.0 %
Niples suppernumerary	16.0 %

Table VII.

Main symptoms and signs in RTS patients	
Genitourinary:	
Testes: incomplete or delayed descent	82.0 %
Criptorchidism	67.0 %
Kidney anomalies or dieseases	50.7 %

Table VIII.

Main symptoms and signs in RTS patients	
Heart:	
Heart murmur	38.9 %
Cardiac defect	33.5 %
Abnormal lobation	27.0 %

Table IX.

Main symptoms and signs in RTS patients	
Neurological defects:	
Mental, motor, languange and social retard	98.5 %
IQ under 50	73.0 %
EEG anomalies	57.6 %
Hyperreflexia	51.0 %
Epilepsy	27.0 %

Discussion

The cause of RTS is still unclear. Recently Hennekham[13] found a microdeletion at 16 p13.3 region in some patients and suggested that deletion is the most probable cause of syndrome. Hennekham documents in 25% of patients affected by RTS this microdeletion[13].

More recently the breakpoint of two distinct reciprocal traslocations occuring in patients with diagnosis of RTS was located in the same band 16 p13.3[5]. However this anomaly cannot be identified in all patients. Clinically the difference between patients with or without deletion is minimal, except microcephaly. Band 16 p13.3 seems to be an important locus for mental retardation in patients with correct diagnosis of RTS.

In our study microcephaly is present in 87% of cases.

In Table XI we have compared with typical clinical manifestations of our study (732 patients) the main symptoms and signs of RTS as summarized by Rubinstein[29] and Smith[33].

It is evident from this table that Smith classification is quite discordant with our data. Infact beaked nose is present in 87% of RTS patients in our study, but only in 68% of Smith patients. On the contrary abnormal ears are present in 73.6% of our study and 94% of Smith classification. Our data seems

Table X. Psychomotor development in children with RTS[29].

Skill	Average month	Range month	Normal range month
Rolled over	7.4	2- 4	2- 5
Crawled	15.3	8- 30	7-10
Sat-up	10.5	6- 30	5- 8
Walked	30.1	15- 54	11-15
First word	25.4	6- 57	9-13
3-words phrases	65	24-156	14-24
Toilet trained	62.5	30-216	24-27
Rode tricycle	67.4	42-216	36-48
Tied shoes	0/50 persons archieved		60-72

Table XI. Comparison of Rubistein and Smith classifications with our study.

Anomaly	Rubistein	Smith	Our meta-analysis
Microcephal	94.0 %	84.0 %	87.0 %
Mental, motor social retard	99.0 %	100.0 %	98.5 %
Stature under 50th percentile	93.0 %	94.0 %	92.7 %
Bone age under 50th	74.0 %	94.0 %	73.6 %
Abnormal ears	81.0 %	84.0 %	75.6 %
Beaked nose	93.0 %	68.0 %	87.0 %
Epicanthi	69.0 %	62.0 %	68.0 %
Palpebral fissures, antimogoloid slant	90.0 %	100.0 %	90.0 %
Strabismus	71.0 %	79.0 %	60.7 %
Narrow palate	93.0 %	100.0 %	93.0 %
Thumbs and toes with broad terminal phalanges	100.0 %	100.0 %	99.0 %
Other finger anomalies	73.0 %	50.0 %	74.0 %

to agree with those by Rubinstein, however microcephaly is present in 87% of our patients, but in 94% of his patients.

With Rubinstein classification the agreement is more complete; the difference stems from the greater number of cases we analyzed, which almost induced a reorganization of some parameters.

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