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A CLASSICAL CASE OF RUBINSTEIN- TAYBI SYNDROME

Paediatrics

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ABSTRACT

Rubinstein–Taybi syndrome (RSTS) is a rare congenital disorder, mainly characterized by postnatal growth retardation, intellectual disability, and facial and limb abnormalities. The syndrome is caused by a mutation in the *CREBBP* or *EP300* gene, or as a result of micro-deletion of genetic material from the short (p) arm of chromosome 16. In some people with RTS, the cause is unknown. While RTS is autosomal dominant, most of the cases result from *de novo* mutation and are not inherited from a parent. Management generally involves screening, growth and developmental monitoring, annual ophthalmologic and hearing evaluations, and evaluation for cardiac, dental and renal anomalies. An echocardiogram should be performed to evaluate for congenital heart disease. Behavioral therapy and special education are also indicated.

KEYWORDS

INTRODUCTION:

Rubinstein-Taybi syndrome (RTS) was first reported by Greek orthopedic surgeons Michail et al. in 1957 as the *broad thumb-hallux syndrome* in "a new case of congenital malformations of the thumbs absolutely symmetrical" and then later in 1963 was described by American physicians, Rubinstein and Taybi, who gave their names to this syndrome, after a more detailed study on seven children with this syndrome[1]. They described a new symptom-complex characterized by broad thumbs and great toes, facial dysmorphism, mental retardation and a group of congenital malformations.

Rubinstein-Taybi syndrome (RSTS) or 6p13.3 deletion syndrome is a rare autosomal dominant genetic disorder with a birth prevalence of 1:100,000 –125,000[2]. Male and female individuals are affected at equal rates.

It is a multisystem developmental disorder characterized by prenatal and postnatal restriction, microcephaly, dysmorphic features, broad thumbs and toes, and intellectual disability. Features include distinctively broad and/or angled fingers and toes, growth and development delay, speech delay, intellectual disability, craniofacial dysmorphism, feeding difficulties, recurrent respiratory infections and urogenital anomalies. In some people, the skin, cardiac or respiratory system may also be affected. Symptoms associated with RSTS vary greatly from person to person.

CASE REPORT:

A 13-year old male, 2nd born to non-consanguineous parents, came to the Department of Pediatrics, Sree Balaji Medical College and Hospital, Chennai with the complaints of undescended testis since birth. The child was born at term via normal vaginal delivery, weighing 2.5 kg and cried immediately after birth with no history of perinatal asphyxia. He has history of delayed development of both motor function and speech with intellectual disability. He has had an episode of seizure at one and half year of age. His elder sister is normal.

On examination, he was found to have:

Short stature (Height -112 cm, < -3 SD according to WHO)
Microcephaly (Head circumference- 48.5 cm)
Intellectual disability: Moderate (IQ - 46)

Dysmorphic facial features- high arched eyebrows, downward slanting of palpebral fissures, strabismus, ptosis, long eyelashes, beaked nose with short low columella, deformed ear pinna, high arched palate, thin upper lip, everted lower lip, malocclusion and multiple caries of teeth, micrognathia
Broad thumb and first toe, flat foot
Micropenis, undescended testis, hirsutism

The child has had a past history of corrective surgeries performed for glaucoma and strabismus in his childhood at the age of 3 years.

The genetic work-up of the child could not be done owing to family's financial constraints.

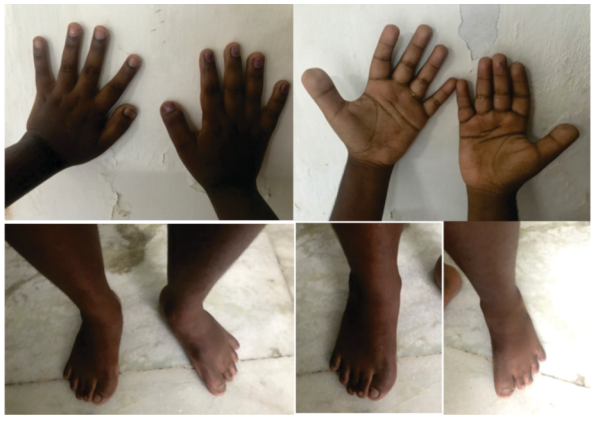

Figure 1 Broad thumbs in hands with broad halluces in feet

Figure 2 High arched eyebrows, downslanting of eyes, ptosis, beaked nose, thin upper lip, malocclusion of teeth, deformed ear pinna, micrognathia, hirsutism

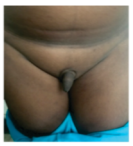
Figure 3
Cryptorchidism


Figure 4
Malocclusion of teeth


Figure 5
Short stature

DISCUSSION:

Rubinstein-Taybi syndrome (RTS) is known to be caused in approximately 10% of the affected individuals by a *submicroscopic deletion* that includes the cAMP response element-binding protein (CREB)-binding protein gene, CREBBP or CBP, located on chromosome 16 at p13.3[3].

Mutation of the CBP gene has been detected in approximately 40% of the affected individuals with RTS. Mutations in another gene, EP300, account for a small number of cases.

Most of *CREBBP* mutations are believed to be de novo heterozygous mutations and as a result, the recurrence rate in a family is low and such families with more than one affected child are extremely rare. Individuals with RSTS rarely reproduce but the risk to offspring is 50%.

Recently, somatic and germ line mosaicism in one of the parents in the postzygotic stage have also been described[4].

Other yet unknown genes may also be responsible for this disorder because approximately 50% of the individuals with clinical features consistent with RTS do not have a detectable deletion or mutation in CBP or Ep300.

Growth and Development:

While prenatal growth is often normal in most infants with RSTS, parameters for height, weight, and head circumference fall below the fifth percentile during infancy. Affected children show failure to thrive in infancy, but may later show a relative obesity for their height. Feeding difficulties like dysphagia can occur and many individuals are prone to repeated respiratory infections. As infants age, they may continue to experience poor growth and exhibit short stature (most below the third percentile).

Most infants and children with RSTS experience varying degrees of intellectual disability with average IQ between 36-51, psychomotor delays, delayed speech and socialization, with delayed developmental milestones. Hypotonia, hyperreflexia, a stiff, unsteady gait, and seizures are also common.

Physical features:

The craniofacial features of a child with Rubinstein-Taybi syndrome are striking owing to microcephaly, prominent forehead, highly arched eyebrows, long eyelashes, downslanting palpebral fissures, broad nasal bridge, hypertelorism, beaking of the nose with the nasal septum extending well below the nares, highly arched palate, a short, thin upper lip, everted lower lip, mild micrognathia and retrognathia, and minor anomalies in shape, position, or rotation of the ears. They have a distinct facial expression of "grimacing" or unusual smile with nearly complete closing of the eyes.

Dental problems like malocclusion or crowding of teeth and multiple caries can occur. Incisors can have talon cusps. Hirsutism is commonly seen. Eye abnormalities may include glaucoma, cataracts, ptosis and strabismus. Few children can suffer from skin problems like keloid formation.

The thumbs are broad and radially deviated. Most infants with RSTS have abnormally broad thumbs and/or great toes as a result of unusual broadness of terminal phalanges. In addition, the distal bones of the thumbs and great toes may also be misaligned on a proximal bone that is abnormally shaped (delta phalanx). Clinodactyly is also commonly seen.

Skeletal Deformities:

Scoliosis, kyphosis, pectus excavatum, abnormalities of vertebrae and pelvis, malformations of ribs, tethering of spinal cord and recurrent dislocation of the knee caps can occur in children with RTS.

Genitourinary:

Male infants with RSTS may have abnormalities of the genitourinary tract including cryptorchidism, hypospadias and shawl scrotum. In addition, infants with RSTS may have hypoplastic or absent kidneys, repeated infections of the urinary tract, renal stones, hydronephrosis, vesicoureteral reflux. In some cases, duplication of the kidneys and/or ureters may also be present.

Cardiac:

Congenital heart disease is seen in one-third of the patients. Patent ductus arteriosus is the most common congenital heart defect present in infants with RSTS. They may also have atrial septal defect, ventricular septal defect, coarctation and stenosis of the aorta, pulmonic stenosis and bicuspid aortic valve[5].

Respiratory:

The lungs may be divided into small extra lobulations. Laryngeal walls may be weak or easily collapsible, potentially resulting in swallowing or breathing difficulties like sleep apnea. This can also cause difficult intubation.

Behavior:

Individuals with RSTS often exhibit a short attention span, decreased tolerance for noise and crowds, impulsivity, and moodiness. Autistic behaviors are common.

Malignant potential:

Some persons with RSTS appear to be more prone to develop neural, developmental and hematological origin tumors including meningioma, pilomatixoma, rhabdomysarcoma, pheochromocytoma, neuroblastoma, medulloblastona, oligodendroglioma, leioyosarcoma, seminoma, odontoma, choristoma, and leukemia than the general population[6,7,8]. However, this is somewhat controversial as one recent study found only an increased risk for meningiomas and pilomatrixomas, but not for malignancies in general.

The prognosis for children with RTS is generally good, but it may vary due to the range and severity of the health problems that may be present. Most patients have developmental delay and intellectual disability but most of the 6-year old children are able to learn to read. Life expectancy generally does not seem to be affected, except in children with complex cardiac defects. Malignancies and respiratory infections are the most common causes of death. Survival rates in general are good and there are many reports of adults with RTS.

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