CLINICAL QUIZ (p266-267) ANSWER

This patient demonstrated dysmorphic features that included down slanting palpebral fissures, low set ears, microcephaly, as well as broad thumbs and toes. Clouding of the cornea due to congenital glaucoma was also apparent. The overall picture was compatible with Rubinstein-Taybi syndrome (RTS).

The patient was referred to the clinical geneticist and sequencing of the *CREBBP* and *EP300* genes was performed. A pathogenic mutation was identified within the *CREBBP* gene on chromosome 16 with a base pair duplication of nucleotide thymine (T) at exon 18 (c.3461dupT). This change is predicted to result in a frame shift of the amino acid sequence and creates a premature stop codon 14 amino acids downstream of the sequence change, therefore truncating the produced CREB-binding protein. His *EP300* gene sequence analysis was normal.

Mutation at *CREBBP* seen in our patient has been reported in other individuals with RTS and our patient's presentations are consistent with the clinical features of RTS.

The incidence of RTS is reported to be 1:100 000-1:125 000 at birth.[1] RTS is inherited in an autosomal dominant pattern and is usually *de novo*. However, there is a 0.1% risk of recurrence due to germline mosaicism. Most patients are suspected of having RTS at birth or during infancy due to the distinctive facial features and characteristic hand and foot findings. RTS is known to affect multiple part of body such as eyes, skin, teeth, musculoskeletal, cardiovascular and urogenital systems. Failure to thrive and learning difficulties are typical associations. In patients with RTS, growth is usually normal antenatally however development slows down significantly during the first few year of life. Average IQ falls in the range of 36 to 51. Obesity may occur during childhood and adolescence. Behavioural problems such as short attention span, hyperactivity, sensitivity to noise and moodiness are also frequently observed. A study has shown an increased autistic behaviour in patients with RTS.[2] However, the expressivity and severity of clinical presentations varies for each individual.

Sixty percent of RTS is attributed to mutation at *CREBBP* gene on chromosome 16p13.3 and 3% to mutation at *EP300* gene on chromosome 22q13.2. Studies suggested RTS is caused by haploinsufficiency of *CREBBP* products that may be due to microdeletion, nonsense, missense and splicing mutation.[3] Research found that mutation at HAT domain of *CREBBP* disrupted the acetylation of histones and reduced the coactivator function of CREB transcription factor.[4] Both *CREBBP* and *EP300* function as tumour suppressor, thus mutation at these regions would also increase the risk of cancer in RTS patients.[5] RTS caused by mutation at *EP300* observed to have a milder phenotype especially in skeletal findings and mental development.[6]

Management of RTS involves a multidisciplinary approach which includes the treatment of manifestation and prevention of secondary complication. Development assessment should be performed every 2 to 3 years from the age of 3 to allow timely intervention with suitable therapies. Please refer to Table 1 for comparison of development milestones of children with RTS to normal children in population. Early intervention programs comprising of speech therapy, occupational therapy, physical therapy and behavioural therapy could be beneficial in helping patient to realise one's full potential. Early ophthalmological assessment is crucial as congenital glaucoma may be difficult to detect initially

Table 1 Comparison of development milestones of children with RTS to normal children in population

Milestone	**Rubinstein-Taybi syndrome**		**Normal children**	
	Average age (months)	**Range**	**Average age (months)**	**Range**
Laughing	2.5	2-6	2	2
Roll over	10	4-18	6	5-7
Sit	16	9-24	7	6-8
Crawl	19	12-36	9	8-10
Stand	29	11-80	9	8-10
Walk	35	18-54	14	12-15

with routine examination. Because of the frequent retinal dysfunction in older children and adults, electrophysiological investigations should be performed every 5 years after 16 years of age. Annual audiology screen is suggested with increased frequency of multiple otitis media observed in patients with RTS. Routine evaluation for cardiac and renal anomalies is also suggested, since 1/3 of RTS patients suffer from some form of congenital heart defects. As mentioned earlier, both *CREBBP* and *EP300* are tumour suppressor genes thus RTS patients are at increased risk of malignancies. Albeit this knowledge, no standard surveillance has been recommended as screening has not been shown to improve outcome. Possibility of tumours should be considered when a RTS patient develops unusual symptoms before the age of 15.[7]

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References

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