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Rubinstein-Taybi Syndrome in a 19-years old boy

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Abstract

INTRODUCTION: Rubinstein-Taybi syndrome is a rare genetic multisystem disorder comprising motor organ dysfunction, craniofacial dysmorphism and psychomotor retardation, frequently with the abnormalities of the thyroid gland.
OBJECTIVE: Presentation of a case of a 19-year-old patient with Rubinstein-Taybi syndrome in whom serum TSH, fT3 and fT4 levels were assessed.
CASE: Craniofacial abnormalities including: microcephaly, underdeveloped maxilla, micrognathia, high arched palate, malocclusion, down-slanting palpebral fissures, thick eyelashes and full eyebrows. Clinodactyly, broad thumbs and toes were observed in the musculoskeletal system. The patient presented with moderate mental retardation, short stature and obesity. Furthermore, I° thoracolumbar scoliosis, elbow joint deformation resulting from the radial head dislocation and limitation of the right hip motion as a consequence of Perthes disease were found. Genetic testing revealed a mutation affecting the CREBBP gene located on the short arm of chromosome 16. The measured serum TSH level was 1.510 μlU/ml (normal range 0.27–4.20), fT3 5.1 pmol/l (normal range 4.1–6.7), fT4 15.5 pmol/l (normal range 13.1–21.3). The patient is subjected to long-term rehabilitation.
CONCLUSIONS: The obtained results of laboratory tests of serum TSH, fT3 and fT4 levels point to a lack of thyroid gland dysfunction in the patient with Rubinstein-Taybi syndrome. Rehabilitation treatment of patients with RTS is necessary to improve the patient's mobility.

CASE REPORT

INTRODUCTION

The Rubinstein-Taybi syndrome (RTS) is a rare genetic congenital anomaly syndrome. It is an autosomal dominant disorder caused by a mutation in CREBBP gene on the short arm of chromosome 16 (16p13.3) and EP300 gene on the long arm of chromosome 22 (22q13) (Petrij *et al.* 1995; Bartsch 2005; Hennekam 2006; Roelfsema & Peters 2007; Zimmermann *et al.* 2007) (Figure 1). In a typical clinical picture of RTS craniofacial anomalies, deformations within the musculoskeletal system with characteristic broad angulated thumbs and halluces and also mental retardation are predominant (Bartsch 2005; Rubinstein & Taybi 1963; Taybi & Rubinstein 1965; Rubinstein 1988).

There are genetic and clinical features suggesting the possibility of the occurrence of thyroid disorders (resistance or hypothyroidism) in the RTS (Rubinstein 1988; Arias 1994; Chakravarti *et al.* 1996; Chrivia *et al.* 1993; Olson & Koenig 1997).

The aim of the study is to present the case of a 19-year-old patient with Rubinstein-Taybi syndrome, in whom serum TSH, fT3 and fT4 levels were determined.

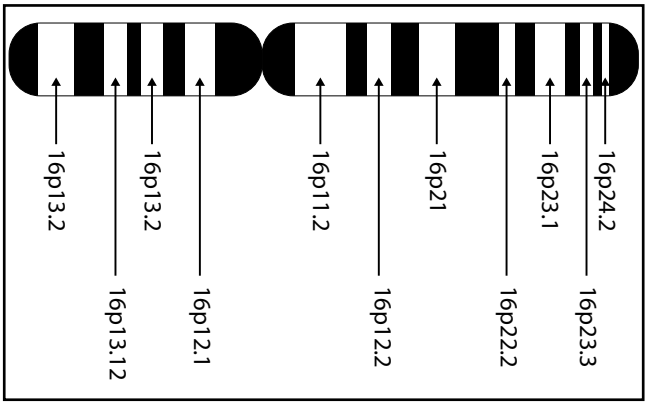

Fig. 1. Autosomal dominant disorder caused by a mutation in CREBBP gene on the short arm of chromosome 16 (16p13.3) and EP300 gene on the long arm of chromosome 22 (22q13).

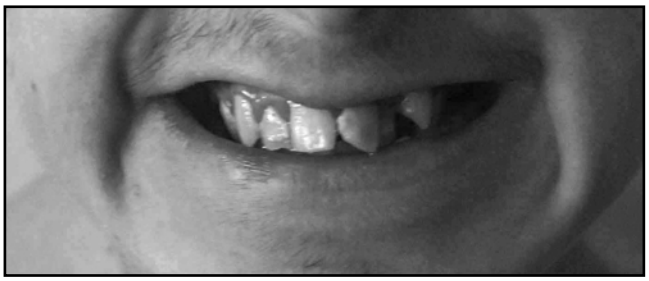

Fig. 2. Faulty bite and set of teeth.

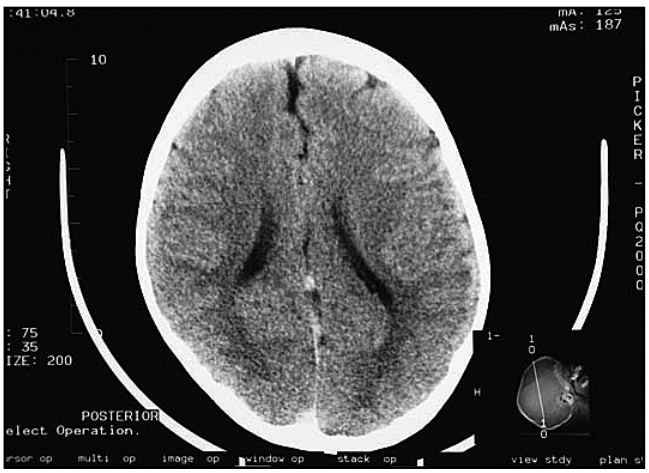

Fig. 3. Features of microcephaly in MRI image.

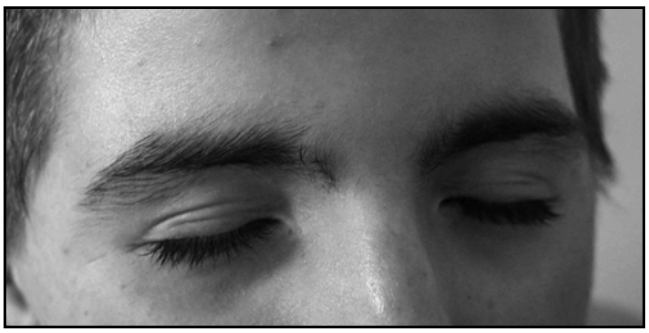

Fig. 4. Typical for the RTS syndrom eyebrows and eyelashes..

CASE REPORT

A male A.M, aged 19 years, undergoing long-term rehabilitation due to numerous deformations and mobility limitations in the musculoskeletal system, which significantly reduced physical and self-care capacity.

The boy was born at term by spontaneous labor. After delivery transposition of the great vessels requiring surgical procedure was detected and shortening of the phalanges in hands and feet.

Genetic tests demonstrated a CREBBP gene mutation located on the short arm of chromosome 16, which allowed to establish the diagnosis of the Rubistein-Taybi syndrome.

The clinical examination reveals growth deficiency and overweight. The patient lacks self-reliance, requires help to perform self-care and daily living activities. Significant motor dysfunction, uses a wheelchair. Exhibits hesitant gait. The problems of communication. Psychological testing confirmed moderate mental retardation. During adolescence he showed features of premature sexual maturation (precocious puberty).

Increased hair growth (hirsutism) on the head, asymmetry of the nasal septum, arched palate, small receding lower jaw (micrognathia), malocclusion and features of microcephaly (Figures 2 and 3). Abnormally full eyebrows and thick eyelashes, characteristic of the Rubinstein-Taybi syndrome (Figure 4).

I° thoracolumbar scoliosis with mobility limitation in this region and thoracic hyperkyphosis are observed. Visible deformity of elbow joints with limited mobility, mainly supination resulting from radial head dislocation (Figure 5). Shortening and thickening of finger

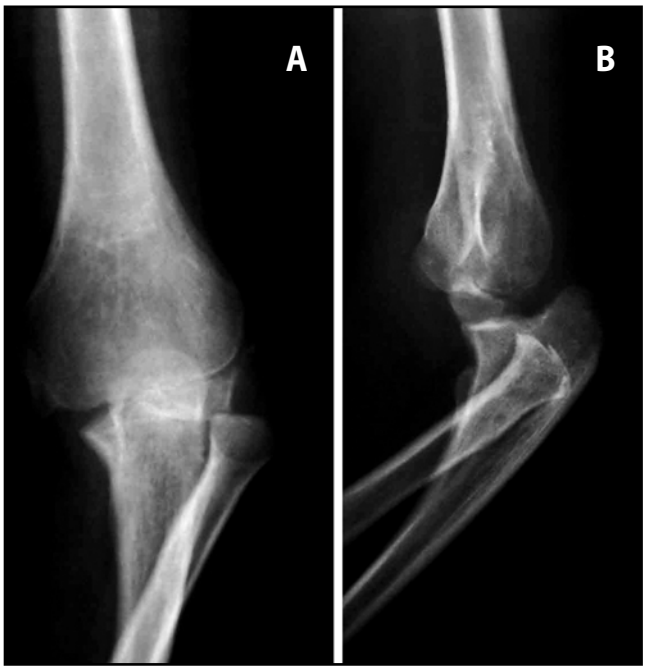

Fig. 5. A: Deformity of the elbow – X-ray image. **B:** Dislocation in the brachio-radial joint – X-ray image.

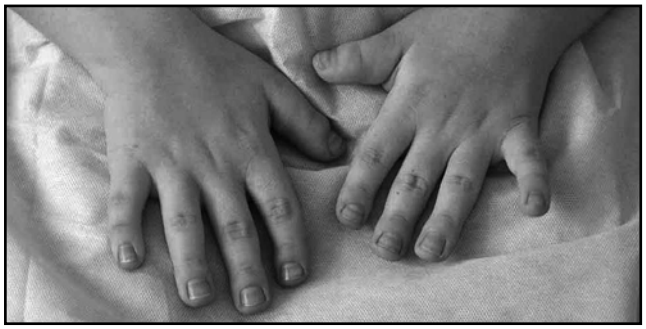

Fig. 6. Deformation of the fingers.

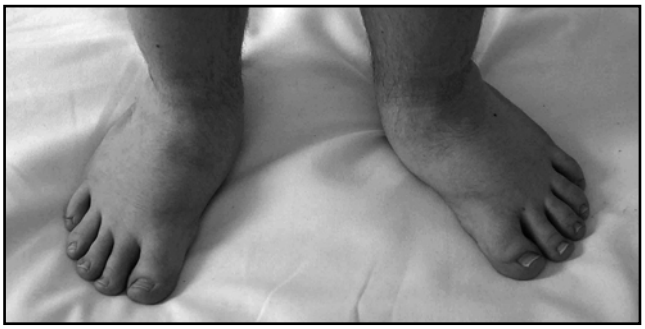

Fig. 7. Feet deformities.

phalanges and a significant radial deviation of the thumb distal phalanges (Figure 6). The mobility of hand joints preserved.

Bilateral knee (25°) and heel (20°) valgity was found. Moreover, longitudinal and transverse arches of both feet are reduced. Toes markedly short and thick. (Figure 7) Normal range of motion in the ankle and metatarso-phalangeal joints. Limited rotation of the right hip joint and lack of hyperextension resulting from Perthes disease.

The patient was supplied with orthopedic shoes and elbow joint stabilizers.

Serum TSH, fT3 and fT4 levels were determined by electro-chemiluminescence immunoassay (Roche ECLIA, COBAS).

The TSH level was 1.510 μlU/ml (normal range 0.27–4.20), fT3 5.1 pmol/l (normal range 4.1–6.7) and fT4 15.5 pmol/l (normal range 13.1–21.3).

DISCUSSION

The patient presented in this report had symptoms characteristic of Rubistein-Taybi syndrome (Rubinstein & Taybi 1963; Taybi & Rubinstein 1965; Rubinstein 1988). Among them obesity, short stature and mental retardation may give a suspicion of congenital hypothyroidism (Olson & Koenig 1997). Also genetic determinants of the syndrome indicate possible dysfunction of the thyroid gland. RTS was found to be caused by mutations in the CREBBP gene (for the CREB-binding protein (CBP)) encoding cAMP response element (Roelfsema & Peters 2007; Olson & Koenig 1997). CBP is a 256 kDa nuclear protein which seems to be a transcriptional coactivator for various signal-transduction pathways i.e. cAMP, nuclear hormone receptors (which include receptors of thyroid hormone), STAT proteins and activated protein – 1. As CBP has been shown to be a critical coactivator for thyroid hormone receptors, abnormally functioning CBP could be expected to cause resistance to thyroid hormones in the Rubistein-Taybi syndrome (Petrij *et al.* 1995; Chakravarti *et al.* 1996; Chrivia *et al.* 1993).

Our observation is consistent with that of Olsen and Koenig. They assumed that the detection of any abnormalities in the functioning of the thyroid gland or the resistance to thyroid hormone might explain the causes of the development of Rubinstein-Taybi syndrome and the application of hormone therapy may improve the functioning of patients with the syndrome by inhibiting the development of certain features dependent on hormonal function of the thyroid gland. The authors examined 12 patients with Rubinstein-Taybi syndrome but none of them had abnormal levels of TSH, fT3 and fT4. Thus the authors concluded that neither hypothyroidism nor thyroid hormone resistance were the typical features of RTS (Olson & Koenig 1997).

CONCLUSIONS

The performed tests of serum TSH, fT3 and fT4 did not deviate from the normal ranges which excludes both hypothyroidism and thyroid hormone resistance. In such cases, moderate TSH elevation can be expected as well as moderate elevation of free T3 and T4 levels. Clinical observations of the patient indicate that proper orthopedic appliances improving the physical fitness and also long-term rehabilitation are of great importance to prevent progression of the disability and to improve his overall performance status.

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