CLINICAL QUIZ (p58) ANSWER

What is the diagnosis?

The clinical features of this child (sparse hair, bulbous nasal tip, thin upper lip, short stature and multiple exostoses) were compatible with Trichorhinopharyngeal syndrome II (TRPSII). Trichorhinophalangeal syndrome (TRPS) is a rare disorder characterised by distinctive craniofacial and skeletal abnormalities, first described in 1966 by Giedion, who named the syndrome on the basis of the three core features: sparse hair, bulbous nasal tip and short/deformed fingers.[1] Under this entity, it contains three subtypes: TRPS I, TRPS II and TRPS III differing in clinical characteristics and pattern of genetic alteration in the *TRPS1* gene (OMIM*604386). All subtypes are characterised by different involvement in craniofacial, ectodermal and skeletal systems TRPS II is featured by multiple exostoses/ osteochondromas and an increased risk of mild-to-moderate intellectual disability. TRPS III is considered an extreme clinical spectrum of TRPS I, with more severe brachydactyly due to short metacarpals and severe short stature. This term may not be used nowadays but may come across in old literature.

In view of multiple exostoses and facial dysmorphic features, our patient is likely suffering from TRPS II. He had chromosomal microarray analysis performed at 2 years of age. The test showed a copy number loss at chromosome 8q23.3q24.12, with a size of at least 6.99 Mb. The deletion encompasses the *TRPS1* and *EXT1* (OMIM*608177). The deletion is de novo. The haploinsufficiency or loss of function mutation of *EXT1* gene is associated with multiple exostoses type 1 (OMIM#133700). *Thus* the diagnosis of TRPS II was substantiated in this child.

The exact prevalence of TRPS is not available in literature.[2] Around 100 cases of TRPS I and TRPS III and 100 cases of TRPS II were published until June 2017.[3] The clinical manifestation is highly heterogeneous. Given the widely variable manifestations, many cases of TRPS probably remain undiagnosed. The condition is rare with estimated prevalence of 0.2-1 per 100,000 without ethnic group difference.[2]

How is the clinical diagnosis established in TRPS?

The diagnosis of TRPS relies on clinical suspicion and pattern recognition. There is no consensus diagnostic criteria for TRPS. TRPS should be suspected if individuals having the following clinical or radiological findings:

Clinical features	**Radiological features**
Characteristic facial features	Cone-shaped epiphyses (detected >2 years old)
Skeletal anomalies	Hip deformities
Ectodermal features (including hair, dental and nails)	Secondary joint degeneration
Intellectual disability*	Multiple osteochondromas*

*Detected in TRPS II only

Characteristic facial features include bulbous nasal tip, long flat philtrum, thin upper lip with vermilion border and protruding ears. Ectodermal anomalies includes slow growing, fine and sparse scalp hair with receded medio-occipital hairline, thin eyebrows, dystrophic nails and dental anomalies, such as supernumerary teeth. Skeletal anomalies include short metacarpals or phalanges (ranging from mild to severe brachydactyly), ulnar or radial deviation of the fingers, swelling of proximal interphalangeal joints (clinobrachydactyly), impaired small joint mobility, joint pain, cone-shaped epiphysis, short stature and osteopenia/decrease in bone mass.[4] Hip deformities, e.g. coxa vara, coxa plana, and coxa magna, Perthes disease-like femoral head changes could be detected in TRPS patients. Secondary joint degeneration Is characterised by joint space narrowing and subchondral sclerosis, involving

hips commonly but also found in other joints. Degenerative changes can be also be present in cervical spine, knees and ankles. Clinical presentation of TRPS could vary widely, from mild change in the phalanges to osteopenia with fragility fractures.

For TRPS II, intellectual disability (usually mild to moderate) and multiple osteochondromas are unique features which are not present in other two subtypes.

Molecular diagnosis of TRPS and Genetic counselling

The diagnosis of TRPS is established in a proband with typical clinical facial features, ectodermal manifestations, limb anomalies together with radiological findings. If the clinical phenotype is not distinct, the molecular diagnosis would be helpful in establishing the diagnosis.

TRPS1 gene is located on chromosomal band 8q24.1. It encodes a transcription factor for a zinc-fingerprotein. It represents a candidate gene for bone homeostasis regulation. It is believed to involve in regulation of bone perichondrium mineralisation and proliferation and apoptosis of chondrocytes.[5]

TRPS I is caused by heterozygous pathogenic variant of the *TRPS1* gene, which leads to haploinsufficiency or loss of function of *TRPS1*. TRPS II, also known as Langer-Giedion syndrome, is a contiguous gene syndrome, caused by a larger deletion in the long arm of chromosome 8 (8q23.3-8q24.11) involving *TRPS1* and *EXT1* genes. The deletion can be detected by chromosomal microarray or even karyotype if the size of deletion is bigger than 5 Mb. *EXT1* appears to have a regulatory effect on longitudinal bone growth and is involved in the development of exostoses. Mental retardation found to be correlated with the size of the interstitial 8q deletion.[6]

TRPS III is a variant of TRPS I, certain missense mutations of the same gene have been described in patients with TRPS III phenotype.[7]

TRPS is inherited in an autosomal dominant manner. The offspring of an affected individual is at a 50% risk of inheriting the pathogenic variant. Once the pathogenic variant has been identified in an affected member, prenatal testing and preimplantation genetic diagnosis for a pregnancy at increased risk are possible. TRPS1 would have 100% penetrance, although expressivity is variable and intrafamilial variation exists.

What are the management issues for TRPS?

Management of TRPS is principally supportive and prefers multi-disciplinary approaches involving pediatric orthopedic, endocrine, genetic, dental, physiotherapy and occupational therapy departments. For ectodermal aspect, advice about hair care and dental care (e.g. extraction of supernumerary teeth) can be given. For skeletal aspect, short stature with or without growth hormone deficiency is major concern. The use of human growth hormone therapy has variable results and would need to be discussed on individual patient's basis. Joint pain is common among TRPS patients. The main stay of treatment is use of analgesic, e.g. NSAID. Physiotherapy may help to improve the joint mobility. Occupational therapy can benefit the fine motor skills or task. In case of severe hip dysplasia, orthopedic surgery, e.g. prosthetic hip implantation can be considered.

Monitoring of linear growth and psychomotor developmental in childhood would be recommended. For TRPS II patients: X-ray evaluation of osteochondromas is recommended when the exostoses are symptomatic and at the time near the end of puberty (when normal growth of osteochondromas has ceased) to provide a baseline for comparison with any future enlargement. Concerning the effect of growth hormone therapy on exostoses development, there is no concrete evidence to conclude it will lead to significant increase in size or number of exostoses.[8] However,careful clinical and imaging follow-up of exostoses is mandatory during the time of growth hormone use.

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