Leri-Weill Syndrome phenotype with atypical cytogenetic finding

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Introduction

Leri-Weill dyschondrosteosis (LWD) is caused by haploinsufficiency of the SHOX gene, located in the pseudoautosomal region (PAR 1) of the short arm of the X and Y chromosomes. The gene is expressed in highest levels in bone tissue and its product likely controls the chondrocyte apoptosis. Deletions and duplications are most frequent, while point mutations are responsible for minority of the cases.

The main clinical symptoms of LWD include disproportionate short stature, mesomorphic shortening of the limbs, Madelung deformity of the forearm and limited wrist movement.

Patients with LWD seem to benefit from growth hormone treatment.

Case Description

History: A 16 years old boy attended the clinic because of short stature. He was born after 3rd uncomplicated pregnancy and delivery, full term, weight 2950 g, length 49 cm. Neonatal period was normal. His first steps and first tooth eruption were at 1 year of age, his first words at 2 years of age. He had frequent respiratory infections. There was no family history of inherited diseases and consanguinity.

Physical examination: W 69 kg, H 150.5 cm, SDS -2.97. Disproportionate short stature with mesomelic shortening of the limbs and Madelung deformity of the forearms. Other findings: micrognathia, thoracic scoliosis, high-arched palate, unilateral cryptorchidism and relatively small testes (12 ml at Tanner V).

Investigations: Biochemistry, thyroid function, gonadotropins, testosterone, IGF-1 - normal. Radiographic changes typical for Madelung deformity were found, the bone age was adequate.

US - left-sided inguinal cryptorchidism. MRI of pituitary region - normal. Karyotype - 45,X[2]/46,X.del(Y)(q11.22)[28]. aCGH Microarray – the interstitial deletion detected by the conventional cytogenetic testing was confirmed: arr[hg19]Yq11.21q11.223[14,698,756-24,504,676)x0(9.81 Mbp]. In addition another deletion was found – arr[hg19]Xq28(154,974,667-155,208,354)x0(0.234 Mbp). Both parents had normal karyotype.

Discussion

We present a patient with typical LWD phenotype but the cytogenetic testing showed deletion in Yq11.2 (PAR 2) while SHOX gene is located in PAR 1 on Yp11.2. A microdeletion in Yp11.2, detection of which is beyond the potential of the conventional cytogenetic testing was considered. aCGH was performed and a 9.81 Mbp interstitial deletion in Yq11.21q11.223 region was confirmed. Only one gene in this region is associated with disorder – the DFFRY gene (OMIM: 400005). Deletions or point mutations are found in men with infertility (Brown et al., Sargent et al., Sun et al., Foresta et al.), but without LWD phenotype. A point mutation of the SHOX gene is another possibility. Another finding was a 0.234 Mbp deletion in the PAR 2 of Xq28 which is with unclear clinical significance. The karyotype of our patient is consistent with mixed gonadal dygenesis and though he is well virilized he has unilateral inguinal cryptorchidism and smaller testes. He will undergo orchidopexy and testicular biopsy. Because of the limited remaining growth potential treatment with growth hormone will not be of benefit.

References: