Leri-Weill Syndrome phenotype with atypical cytogenetic finding

V. Mladenov, V. Iotova, L. Angelova, M. Stoyanova, V. Bogdanova

UMHAT "Sveta Marina", Varna, Bulgaria; Medical University, Varna, Bulgaria

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, mesomelic shortening of the limbs, Madelung deformity of the forearm and limited wrist movement.

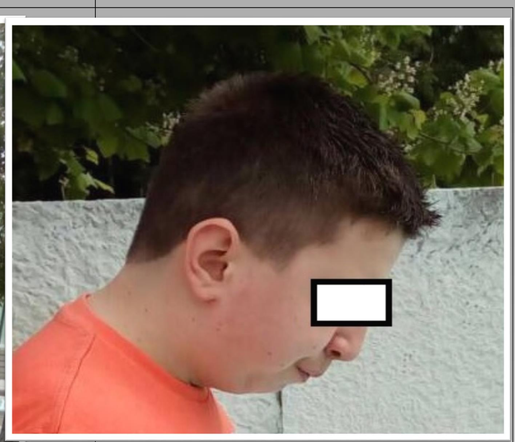
Patients with **LWD** seem to benefit from growth hormone treatment.

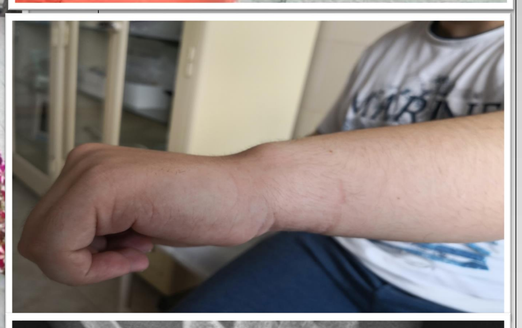
Case Description

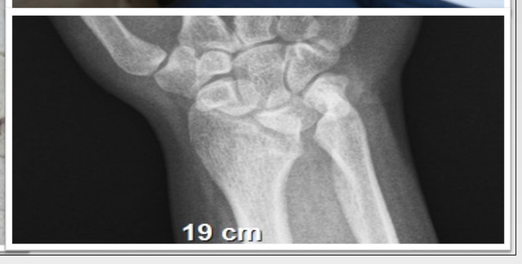
History: A 16 years old boy attended the clinic because of short stature. He was born after 3rd uncomplicated pregnancy and delivery, full term, weight 2950 g, lenght 49 cm. Neonatal period was normal. His first steps and first tooth eruption were at 1 year of age, his first words at 2 years of age.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

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).

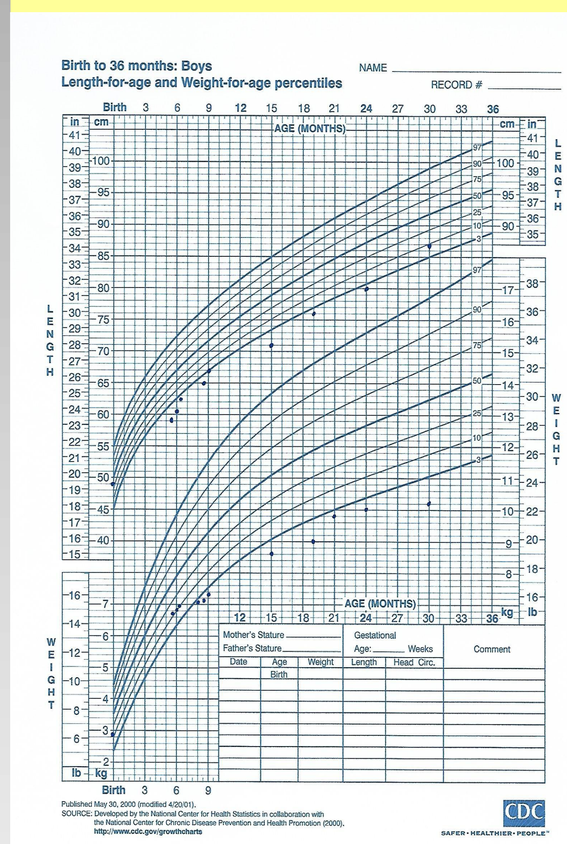
Investigations: Biochemistry, thyroid function, gonadotropins, testosterone, IGF-1 - normal. Radiographic changes typical for **Madelung deformity** were found, the bone age was adequate. **US** - left-sided inguinal cryptorchidism. **MRI** of pituitary region - normal. **Karyotype** - **45,X[2]/46,X,del(Y)(q11.22)[28]**. **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.

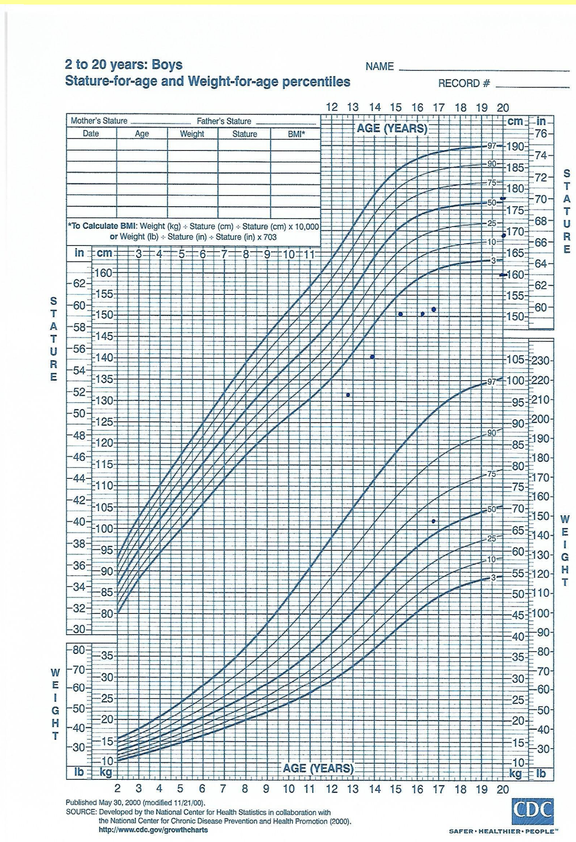






Growth





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 dysgenesis 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:

1. Rappold, G. A., Ross, J. L., Blaschke, R. J., and Blum, W. F. Understanding SHOX deficiency and its role in growth disorders: A reference guide. TMG Health Care Publications, Oxfordshire, UK, 2002
2. Brown, G. M., Furlong, R. A., Sargent, C. A., Erickson, R. P., Longepied, G., Mitchell, M., Jones, M. H., Hargreave, T. B., Cooke, H. J., Affara, N. A. Characterisation of the coding sequence and fine mapping of the human DFFRY gene and comparative expression analysis and mapping to the Sxr-b interval of the mouse Y chromosome of the Dffry gene. Hum. Molec. Genet. 7: 97-107, 1998.
3. Sargent, C. A.., Boucher, C. A., Kirsch, S., Brown, G., Weiss, B., Trundley, A., Burgoyne, P., Saut, N., Durand, C., Levy, N., Terriou, P., Hargreave, T., Cooke, H., Mitchell, M., Rappold, G. A., Affara, N. A. The critical region of overlap defining the AZFa male infertility interval of proximal Yq contains three transcribed sequences. J. Med. Genet. 36: 670-677, 1999.
4. Sun, C., Skaletsky, H., Birren, B., Devon, K., Tang, Z., Silber, S., Oates, R., Page, D. C. An azoospermic man with a de novo point mutation in the Y-chromosomal gene USP9Y. Nature Genet. 23: 429-432, 1999.
5. Foresta, C., Ferlin, A., Moro, E. Deletion and expression analysis of AZFa genes on the human Y chromosome revealed a major role for DBY in male infertility. Hum. Molec. Genet. 9: 1161-1169, 2000.

57ESPE 261--P3

Growth and syndromes (to include Turner syndrome)

Vilhelm Mladenov

Poster presented at: 57th ESPE 2018 Meeting ATHENS GREECE 27-29 September 2018

PosterSessionOnline.com