LETTER TO THE EDITOR

A BOY WITH SHORT STATURE, UNUSUAL FINDINGS AND LOW PERCENTAGE OF 45,X(4%) / 46,XY(96%) MOSAICISM

BY M. DOGAN [1], R. EROZ [1], S. BOLU [2], H. YUCE [1] AND E. GUN [3]

45,X/46,XY mosaicism is a rare disorder of sexual development and assumably underdiagnosed condition, and it has an incidence as 1.5 per 10.000 newborns (4). This condition is caused from chromosomal missegregation during early embryonic mitosis, through interchromosomal rearrangement or anaphase lag. It occurs as de novo and it could be favored by an abnormal structure of the Y chromosome (6).

45,X/46,XY mosaicism can be seen in cases with normal male external genitalia. This phenotype is generally related with bilateral testes and possible higher number of the cell line with 46,XY in the gonads (9). It was reported that, men with the 45,X/46,XY chromosomal composition have a raised risk for germcell neoplasia of the gonads and the cases with genital ambiguity have higher tumor risk (3). There is no clear prediction of tumor risk in cases with 45,X/46,XY who have a normal male appearance but Cools reported the low risk due to normal external masculinisation score and bilaterally descended testes (2).

There was no correlation between percentage of evaluated lymphocytes cells with 45,X and the severity of ambiguous genitalia or final height (4, 1, 7).

We report a 14 years and 9 months old patient with a normal male phenotype also presenting with few of Turner syndrome stigmata. 45,X/46,XY mosaicism was detected. The patient was referred to our clinic by pediatric endocrinology because of unexplained short stature. He had Turner-like appearance (broad chest with widely spaced nipples, short stature, cubitus valgus, mild nail dysplasia, renal anomaly). The patient's height was 148cm (<3p), his weight was 49 kg (3-10p), the head circumference was 51.0 cm (<3p). Height potential prediction by mid-parental height was 176.5 cm, thus the patient was 28.5 cm shorter than his target height. His projected height was 163 cm. He was from a Turkish ethnic group. He had a healthy sister and a healthy brother. There was no relationship between parents. His mother's and

(1) Department of Medical Genetics, Duzce University, Duzce, Turkey.

(2) Department of Pediatrics, Division of Pediatric Endocrinology, Duzce University, Duzce, Turkey.

(3) Department of Pediatrics, Duzce University, Duzce, Turkey.

father's age were 42 and 39 years old, respectively. He was born at 31 weeks gestation with a birth weight of 2100 gr by cesarean section due to fetal distress. There was no asphyxia story during birth but he was taken in a couveuse after birth for better nutrition.

He had no history of seizures. The patient had mild mental retardation, his school performance was poor. In the physical examination of our case, he had scoliosis, a scar trail over the left clavicle, cervical asymmetry, short neck, round shaped face, broad nasal root and bridge, upslanting palpebral fissures, synophrys, bushy eyebrows, bulbous nose, anteverted nostrils, high arched palate, malar hypoplasia, dental malocclusion, thin lips, cubitus valgus, simian crease in his left hand, mild hypoplastic nails. He had no vision defects and any hearing problems. Pediatric echocardiography examination was normal. According to abdominal ultrasonography extra renal pelvis view in the left kidney, also double collecting system was seen in the right kidney. Pelvic USG was normal. Routine serum and urine biochemical analysis were in the normal range. From his past medical history, he had congenital torticollis and operated on at 9 years of age. At the moment he had cervical asymmetry, mild short neck and scoliosis.

He had normal male external genitalia with a normal penis, marked pubic hair (Tanner stage 3) and there were two palpable testis, each with a volume of 8 mL (tanner stage 2) at ultrasound. Total testosterone serum concentration was 80.78 ng/dl and it is in normal range for tanner stage 2. According to scrotal ultrasound both testis were in normal pubertal size and parenchymal echo is homogeneous. Two anechoic cysts were detected at the right epididymal head localization and the large one is 2x3 mm size. Regular monitoring is essential in these anechoic cysts.

Laboratory analysis results showed basal levels of FSH, LH, Estradiol, Cortisol, Prolactin, 1.4-androstenedione, DHEAS, TSH, free T4 all within the normal range. Also the levels of alpha-fetoprotein and β-hCG were normal range. Bone age was estimated at 13 years and 9 months. Skeletal maturation was retarded by 1 year. The lower level of insulin-like growth factor 1 (IGF-I 285 mg/dl) and basal level of the normal limits of IGF-BP3 (4.7 mg/dl) were detected. So L-dopa provocation test was done and maximum response was measured as 9.68 ng/ml. After this result, a second growth hormone stimulation test was planned. According to the results, pediatric endocrinology will begin Growth Hormone (GH) treatment to the patient if required.

In a recent study, it was reported that a potential link exists between 45,X/46,XY mosaicism and hypothyroidism (5), but our patient has normal thyroidal functions.

Laboratory analysis showed no evidence of a chronic disease. Because predicted adult height of our case was below according to the mid-parental height, a chromosomal analysis was performed. Karyotype analysis of the case was detected as 45,X(4) / 46,XY(46). So SRY FISH analysis was carried out and, 4% (8 of the analyzed cells) X and %96 (192 of the analyzed cells) XY signal pattern were determined. Also the analysis of Y chromosome microdeletions for AZF-A, AZF-B, AZF-C genes were performed but no deletion was found.

It should be kept in mind that the peripheral blood cells' karyotype doesn't predict the chromosome constitution of other body tissues (8) and phenotypic features are independent of the percentage of 45,X cells in the lymphocyte karyotype.

In our case, the different phenotypic features such as synophrys, bushy eyebrows, bulbous nose were observed. Turner-like appearance are also uncommon clinical features in boys with this mosaicism. Additionally our patient had learning difficulties, another rare finding in boys with 45,X/46,XY karyotype. We offer an interesting case in this regard and we have mentioned in detail the patient's clinical profile.

Although our case had a low percentage of a mosaicism on peripheral blood, he had clinical findings related with this karyotype and this situation can be explained by the ratio of mosaicism being different in other tissues. Early karyotype analysis in children with short stature can provide early detection of the mosaicism, thus more effective treatment strategy for the management of the disease can be performed. In order to obtain more accurate information about 45,X/46,XY mosaicism, further studies are needed to be done for the current topica.

REFERENCES

1. *BOGUSZEWSKI M.C., MERICQ V., BERGADA I., DAMIANI D., BELGOROSKY A., GUNCZLER P., ORTIZ T., LLANO M., DOMENÉ H.M., CALZADA-LEÓN R., BLANCO A., BARRIENTOS M., PROCEL P., LANES R., JARAMILLO O.:* Latin American consensus: children born small for gestational age. *BMC. Pediatr.,* 2011, *11*, 66.
2. *COOLS M., PLESKACOVA J., STOOP H., HOEBEKE P., VAN LAECKE E., DROP S.L., LEBL J., OOSTERHUIS J.W., LOOIJENGA L.H., WOLFFENBUTTEL K.P.:* Gonadal pathology and tumor risk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism. *J. Clin. Endocrinol. Metab.,* 2011, *96*, E1171-E1180.
3. *DENDRINOS M.L., SMORGICK N., MARSH C.A., SMITH Y.R., QUINT E.H.:* Occurrence of Gonadoblastoma in Patients with 45,X/46,XY Mosaicism. *J. Pediatr. Adolesc. Gynecol.,* 2015, *28*, 192-195.
4. *FABIANO R., ROSA M., FRANCISCO W., BARTEL D., DIBBI R.P., CARDOSO R., ROSAL M., TREVISAN P., GRAZIADIO C., PASKULIN G.A., RICARDO P., ZEN G.:* 45,X/46,XY mosaicism: report on 14 patients from a Brazilian hospital. A retrospective study. *Sao. Paulo. Med. J.,* 2014, *132*, 332-338.
5. *HOJAT L., SCHWEIGER M.:* 45,X/46,XY Mosaicism and possible association with hypothyroidism

in males. *Clin. Pediatr. (Phila.),* 2015, *e-pub ahead of print*. Doi: 10.1177/0009922815600439

6. *HSU L.Y.:* Phenotype/karyotype correlations of Y chromosome aneuploidy with emphasis on structural aberrations in postnatally diagnosed cases. *Am. J. Med. Genet.,* 1994, *53*, 108-140.

7. *MARTINERIE L., MOREL Y., GAY C.L., PIENKOWSKI C., DE KERDANET M., CABROL S., LECOINTRE C., COUTANT R., BARON S., COLLE M., BRAUNER R., THIBAUD E., LEGER J., NIHOUL-FEKETE C., BOUVATTIER C.:* Impaired puberty, fertility, and final stature in 45,X/46,XY mixed gonadal dysgenetic patients raised as boys. *Eur. J. Endocrinol.,* 2012, *166*, 687-694.

8. *TOSSON H., ROSE S.R., GARTNER L.A.:* Children with 45,X/46,XY karyotype from birth to adult height. *Horm. Res. Paediatr.,* 2010, *74*, 190-200.

9. *TOSSON H., ROSE S.R., GARTNER L.:* Description of children with 45,X/46,XY karyotype. *Eur. J. Pediatr.,* 2012, *171*, 521-529.

ADDRESS FOR CORRESPONDENCE:

Dr. Mustafa DOGAN (MD),
Department of Genetics
Duzce University Medical School
81820
TURKEY.
Tel: +90 5414785969; Fax: +90 380 5421302
E-mail: mustafadogan81@yahoo.com