Characteristic of children with mixed gonadal dysgenesis

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OBJECTIVES

Mixed gonadal dysgenesis (MGD) is a DSD with variations of 45,X/46XY karyotype detected in 1,7/10000 newborns. Patients' phenotype varies from Turner syndrome (TS) females to children with ambiguous genitalia or normal male development. Gender assignment and further management of such patients is difficult and sometimes controversial.

METHODS

We have described and retrospectively analyzed the features of 6 MGD patients (3 raised as boys and 3 as girls) followed-up by paediatric endocrinologists in our institutions.

RESULTS

Table 1 Patients' neonatal presentation, sex assignment , karyotype , age and type of genital surgery performed

Pt ID	External genitalia/ ambiguity at birth	Sex assignment at birth/ reassignment, years	Age at karyotyping, years	Reason for karyotyping	Karyotype	45,X cells, %	The first visit to endocrinologist , years	Age (years) and type of genital surgery
1	penile hypospadias, gonads both scrotal	M/ -	In utero	maternal age	45,X/ 46,X,der(Y)	10	4,0	4,0; hypospadia correction
2	left gonad inguinal, right scrotal	M/-	In utero	maternal age and thyroid cancer	45,X/ 46,X,idic(Y)	77	4,0	-
3	normal penile length, gonads both scrotal	M/-	9,5	poor linear growth and obesity	45,X/ 46,X,r(Y)	66	8,5	-
4	female	F/-	10,4	poor linear growth	45,X/ 46,X+invdup(Y)	55	10,4	10,4; bilateral laparoscopic streak-gonads removal
5	scrotal hypospadias, bilateral chriptorchidism, ectopic testis suspicious	M/ F, 2	just after birth	ambiguous genitalia	46,XY at birth; 45,X/ 46,XY - 2 years	30	2,0	2,0; hypospadias correction, removal of dysgenetic inguinal testis on the right; at abdominal laparoscopy ovary and uterine tube found on the left, not removed
6	female	F/-	10,0	poor linear growth	45,X/ 46,X,i(Yp)	NA	10,0	10,4; bilateral laparoscopic streak-gonads removal

Table 2 Patients' growth, puberty course and other clinical features

Pt ID	Current age, y.	MPH, SDS	Age,y./ height, SDS at GH start	Duration of GH treatment, mo.	Age of puberty start, y.	Height at last exam, cm/SDS	Testicular volume, ml/ uterine size x age at last exam	Last LH/FSH, mIU/l	Other findings
1	16,6	-0,5	12,0/ -1,75	18*	12,0 spontaneous; testosterone replacement after 16 y.	159/ -2,3	10 ml both	5,7/10,9	IUGR; testicular microlitiasis at US; arrested puberty (testicular size 10 ml by the age of 16); azoospermia; pituitary microadenoma and Rathke's pauch small cyst by MRI
2	6	+1,5	-	-	-	104/ +1,0	2 ml right	0,6/0,9	hydronephrosis of the right kidney, surgery at 6 mo. after birth
3	13,3	+1,5	11,8/ -1,25	17	11,6 spontaneous	151/ -0,5	11ml right, 10ml left	2,5/2,4	primary hypothyroidism due to AIT with L-T4 replacement; metabolic obesity
4	14,8	+1,5	10,7/ -1,0	48	13,0 induced	150,3/ -1,75	uterus x 11 y.	10,7/34,3	IUGR, TS-like phenotype with poor growth after 4 y., horseshoe kidney
5	12,2	+0,5	10,6/ -1,0	18*	12,2 induced	146/ -0,5	uterus x 8 y.	4,8/42,5	IUGR, weight excess, IGT, cholesteatoma
6	12,4	-0,25	10,6/ -2,25	12	-	123,5/ -1,5	uterus x 5 y.	5,5/47,1	IUGR, TS-like phenotype with poor growth after 3 y., primary hypothyroidism, horseshoe kidney, minor cardiac anomaly; pituitary hypoplasia by MRI

* - GH treatment was interrupted due to bone age rapid acceleration

CONCLUSIONS

In MGD children, 45,X cells clone, due to the *SHOX* gene haploinsufficiency, is responsible for TS-like phenotype and poor linear growth.
Structure rearrangements of the Y-chromosome in 45,X/46,XY mosaicism.lead to decreased androgenization of the fetus, arrested puberty, impaired spermatogenesis in boys. In both sexes, dysgenetic gonads require surgical removal due to very high risk of malignancy(30% of gonadoblastoma risk in girls; 10% - of malignancies in boys, even phenotypicly normal!). Sex hormone replacement therapy for puberty induction/ completion/ infertility and ART need are common problems in MGD patients of both sexes since adolescence through adulthood.
Even phenotypicly normal MGD male may have somatic anomalies, poor growth and fertility.
Taking into consideration all the above, patients with 45,X/46,XY karyotype require closed follow-up by DSD specialists' team for life.

The authors have nothing to disclose

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