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45,X/46,XY qh– KARYOTYPE AND ASPERMIA. A CASE REPORT

A 41-years old male with short stature, abnormal male sex differentiation, aspermia and schizoid character disorder is described. The patient was studied from clinical, endocrinological and genetic perspectives. Cytogenetical analysis revealed a chromosomic mosaicism formed by two normal lines 45X and 46,XY qh–. Molecular studies on AZF region evidenced that it was conserved. The correlation of the symptoms with the cytogenetic finding is discussed.

Introduction. Turner syndrome is one of the most common types of aneuploidy among humans and is present in 1:2000 newborns with female phenotype. Cytogenetically the syndrome is characterized by sex chromosome monosomy (45 X) which is present in 50–60 % of the cases. The other cases present mosaicism with a 45 X cell line accompanied by one or more other cell lines with a complete or structural abnormal X or Y chromosome. Around 5 % are accounted for by patients with structural abnormalities of the Y chromosome (isochromosomes of the long arm and dicentric chromosomes) and mosaics that include a cell line accompanied by others with at least one Y chromosome, whether complete or not [1]. These patients are at increased risk for germ cell tumors and gonadoblastomas. Individuals with Turner syndrome present extremely variable phenotypes.

Approximately 13.7 % of infertile men with aspermia and 4,6 % with oligospermia have a co-existent chromosome abnormality [2]. According to previous studies correlating clinical and cytogenetic findings in cases with deletion of the long arm of the Y chromosome, the following genes are assumed to exist on the euchromatic region of Yq: those influencing spermatogenesis (adjacent to the Yq heterochromatin), those responsible for the body growth (proximally to those for spermatogenesis) and male determining genes (close to the centromere) [3–5]. Mutations in genes present in Y chromosomes can cause abnormalities of testis determination or disorders of sex differentiation leading to 46, XY disorders of sex development [6].

Material and method. The patient, a 41-year-old male, was the third child of healthy parents. His father died at the age of 79, he suffered from a prostate carcinoma. One of his brothers died from acute myocardial infarction. His mother is still alive (81 years old), as well as one healthy brother and one healthy sister. At birth he showed right inginal cryptorchid testis, hypospadias and growth retardation. Cytogenetic studies indicated that the patient had a 45,X/46,XYqh– karyotype (Fig. 1), chromosomal constitution compatible with asymmetrical gonadal differentiation. His father was studied, proving that he had a Y chromosome with the characteristic heterochromatic bloc. Thus the child presented a chromosomic mosaicism. The patient underwent surgical treatment before 2 years of age, which is the time

Fig. 1. Karyotype 45,X(5)/46,XY qh−(18). Cytogenetic evaluation-Chromosome analysis was performed on peripheral lymphocytes with G-banding; 23 metaphases were analyzed. The patient presented a chromosomic mosaicism formed by two normal lines 45X(5)(left) and 46,XY qh−(18)right. Note the Y-chromosome short arm

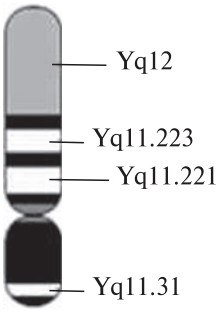

Fig. 2. Y-chromosome. According to the PCR studies the AZF region is conserved, so the deletion should be located far beyond Yq11,23

when the child becomes aware of his/her genitals and social sex. The aim of surgical treatment was to allow development of adequate external genitalia and remove internal structures that are inappropriate for the social sex. Surgery consists in orthophaloplasty, scrotumplasty, proximal and distal urethroplasty and orchidopexy Secon dary sexual characteristics appeared at the age of 12−13.

Clinical Data. Physical examination revealed a weight of 150 cm, weight of 49,300 g, Body Mass Index: 22. Normal cardiovascular system, arterial pressure: 100/60, cardiac frequency: 88 beats/min. Euthermic and normohydrated skin. Respiratory tract: good ventilation without added noises. Soft abdomen, depressible, not painful. Schizoid character disorder.

Endocrinological Profile. Laboratory data were normal except for plasma LH 18.0 mUI/ml (normal range 1,4−7.7), FSH 50.1 mUI/ml (1.5−14) and bioavailable testosterone 1,73 ng/ml (normal range: 2,3−3,9). The patient had normal values for total testosterone 4,7 ng/ml (RIA; normal range: 2,8−8,8) and sex hormone-binding globulin (SHBG): 48,7 nmol/l (normal range: 11−70).

Urology. Hair distribution according to male sex. Daily shave frequency. Penis: 6×3×2 cm. Right testis 8,8 ml, left testis 9,9 ml. No gynecomastia. The patient had satisfactory sexual erection but no-ejaculation. No sperm were found in the post-erection urine. Ultrasonography revealed an atrophic right testis and a left one with microcalcifications, prostate of 10 cm^3 and normal seminal vesicles. Abdominal pelvis tomography with oral and endogenous contrast and deferent-vesiculography, transrectal transductor ultrasound was ordered to the patient to reveal if the via for sperm exit is present but he refused the proposal claiming that it was invasive. He was also asked for serum subunit b-human chorionic gonadotropin, alpha feto protein and lactic dehidrogenase dosages to discard tumorigenesis due to his basic profile (Results: negative, 1,5 UI/ml and 231UI/l ; Reference values: negative, 0−4 UI/ml and 230−460 UI/l respectively).

Assessment of AZF microdeletions. In peripheric blood 5 multiplex polymerase chain reaction (PCR) that determine 28 loci Yq11 in the regions A,B and C associated with spermatogenesis and 2 multiple PCR that determine proximal and distal loci to the AZFa region were assayed.

PCR I	PCR II	PCR III	PCR IV	PCR V
SY84	SY143	SY86	SY14(SRY9	Y6H34pr
SY134	SY157	SY105	SY95	FR15-IIpr
SY117	SY81	SY82	SY127	Y6HP52pr
SY102	SY182	Y6HP35pr	SY109	Y6HP35pr
SY151	SY147	Y6PHC54pr	SY149	Y6d14pr
SY94		SY153		
SY88		SY97		

Study on the proximal and distal AZFa region: AZFa-PROX1 +; AZFa-PROX2 +; AZFa-DIST1 +; AZFa-DIST2 +.

The primers of the 5PCR were as follows (Table). No evidence of microdeletions in the analyzed loci was found. With the methodology employed the 95 % of the microdeletions associated to spermatogenesis defects are detected. Then the defect could not be attributed to AZF microdeletions (Fig. 2).

Discussion. Neoplastic transformation of germ cells in dysgenetic gonads (gonadoblastomas and/or invasive germ cell tumours) occurs in 20−30 % of 46, XY DSD patients, and is associated with the presence of Y chromosome or part of it. The presence of a well defined part of the Y chromosome, known as the gonadoblastoma Y locus (GBY) is a prerequisite for malignant transformation. Among the genes located on the GBY region the TSPY seems to be the most significant candidate gene for tumor-promoting processes [7]. Besides his cytogenetical pattern, the patient presented testicular microlithiasis, an uncommon condition characterized by calcifications within the seminiferous tubules that was associated with the development of testicular cancer [8]. Due to his biochemical profile and his clinical exam we could discard up to the moment cancer tumor in this patient.

The patient is aware of his genetic pattern since early childhood. At adulthood he consults for alopecia and is particularly worried about his aspermia. Aspermia may be defined as a condition in which the male is able to perform coitus properly, but no semen is ejaculated. Aspermia may be either absolute or temporary, congenital or acquired. The noemission may be due to a failure of the reflex act of ejaculation in response to mechanical stimulus of coito; it may be caused by alteration in the seminal passages which prevents its entrance into the urethra or by some mechanical obstacle in the urethra which obstructs its outward flow. Retroejaculation may also be cause of aspermia. This patient has absolute aspermia of congenital etiology. Although we found no sperm in the post-masturbation urine, retroejaculation may not be discarded, due to the high levels of serum gonadotrophins; in spite of the fact that the AZF [9] is conserved, spermatogenesis appears to be absent. The fact that this patient has a Turner syndrome complicates efforts to distinctively correlate the deletions in the Y chromosome with his infertile phenotype, mainly aspermia. After a complete review of the literature, there is strong support of the existence of factors involved in aspermia codified in the deleted Yq chromosome [5, 10−12]. This hypothesis should be further studied using knock-out mice. Our aim to describe this particular case is because we believe that detailed clinical phenotypes may help to understand new undisclosed biochemical pathways involved in the genetic causes of male factor infertility [13].

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45,X/46,XY qh− КАРИОТИП И АСПЕРМИЯ. ОПИСАНИЕ СЛУЧАЯ

Пациент 41 года, с задержкой роста, аномальным развитием мужских половых признаков, аспермией и шизоидным типом темперамента был изучен в отношении клинических, эндокринологических и генетических параметров. Цитогенетический анализ показал хромосомный мозаицизм, полученный от двух нормальных линий 45X и 46,XY qh−. Молекулярный анализ локуса AZF показал, что он был сохранен. Обсуждается корреляция симптомов с цитогенетическими данными.

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45,X/46,XY qh− КАРІОТИП ТА АСПЕРМІЯ. ОПИС ВИПАДКУ

Пацієнт 41 року, із затримкою росту, аномальним розвитком чоловічих статевих ознак, аспермією і шизоїдним типом темпераменту був досліджений відносно клінічних, ендокринологічних і генетичних параметрів. Цитогенетичний аналіз показав хромосомний мозаїцизм, отриманий від двох нормальних ліній 45X і 46,XY qh−. Молекулярний аналіз локуса AZF показав, що він був збережений. Обговорюється кореляція симптомів з цитогенетичними даними.

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