Original article

45,X/46,XY mosaicism: Report of five cases and clinical review

Mosaïcisme 45,X/46,XY : à propos de cinq cas et revue de littérature

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Résumé

Introduction. – Le mosaïcisme 45,X/46,XY est une anomalie gonosomique du déterminisme sexuel caractérisé par un très large spectre phénotypique allant de femmes avec ou sans stigmates turnériens, aux hommes d’apparence normale en passant par les phénotypes ambigus avec un degré variable de masculinisation des organes génitaux externes. Du point de vue histologique, plusieurs situations peuvent se présenter. Patients et méthodes. – Nous rapportons cinq observations de patients ayant un mosaïcisme à caryotype 45,X/46,XY. Nous avons analysé les données cliniques, biologiques, échographiques et génitographiques ainsi que les constatations peropératoires et le traitement effectué chez ces patients. Résultats. – L’âge moyen de nos patients était de 6,6 ans, deux avaient un phénotype féminin avec hypertrophie clitoridienne (dont l’une d’elles avait stigmates turnériens), un avait un phénotype masculin normal avec cryptorchidie bilatérale et deux une ambiguïté des organes génitaux externes, ces deux derniers ont été assignés au sexe masculin. Un retard statural était noté chez quatre patients. L’exploration chirurgicale a permis de retenir le diagnostic de dysgénésie gonadique mixte chez quatre de nos patients. Aucun cas de gonadoblastome n’a été rapporté, chez les deux filles une gonadectomie prophylactique a été réalisée, chez les garçons la streak gonade a été réséquée et le testicule dysgénétique biopsié et préservé sous réserve d’une surveillance assidue. Conclusion. – Cette hétérogénéité souligne l’importance d’une évaluation clinico-histologique précise chez tout patient présentant un caryotype 45,X/46,XY.

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Mots clés : Dysgénésie gonadique mixte ; Mosaïcisme 45, X/46, XY ; Phénotype ; Syndrome de Turner ; Anomalies du chromosome Y

Abstract

Introduction. – The mosaicism 45, X/46, XY is a gonosomal abnormality characterized by a broad phenotypic spectrum, ranging from women with or without Turner syndrome stigmata, to men apparently normal, passing by the ambiguous phenotypes with variable virilisation of external genitalia. From the histological point of view, several situations may arise. Patients and methods. – We analyzed the clinical, hormonal, sonographic, and genitographic data, as well as peroperative and histological findings for five cases of mosaicism 45, X/46, XY, and we discussed treatment performed. Results. – The mean age of patients was 6.6 years, two had a female phenotype with hypertrophy clitoridienne (one of them had Turner syndrome stigmata), one had a normal male phenotype with bilateral cryptorchidism and two had an ambiguity of external genitalia assigned to male. Short stature was noted for four patients. Surgical exploration concluded to the diagnosis of mixed gonadal dysgenesis for four of our patients. No cases of gonadoblastoma have been reported, for girls a prophylactic gonadectomy was performed, for boys the streak gonad was resected and the dysgenetic testis biopsied and preserved, subject for constant monitoring. Conclusion. – This heterogeneity indicate the importance of an accurate clinical and histological evaluation of any patient presenting with 45, X/46,XY mosaicism. © 2011 Elsevier Masson SAS. All rights reserved.

Keywords: Mixed gonadal dysgenesis; 45, X/46, XY; Phenotype; Turner’s syndrome; Y chromosome abnormalities

1. Introduction

Mosaicism is defined by the presence in the same individual, of two or more cell populations derived from a single stem cell line, but with a different composition of chromosomes.
45,X/46,XY mosaicism is an extremely rare disorder, its incidence for the general population varies between 1.5/10,000 and 1.7/10,000 depending on the series [1,2]. It combines a very wide range from phenotypic women with and without Turner syndrome stigmata, to men apparently normal through the ambiguous phenotypes with varying degrees of masculinisation of external genitalia. With this karyotype, histological abnormalities are present in 27% of men with normal masculinisation of external genitalia [2]. In addition to the almost constant persistence of Mullerian ducts, several situations may arise: normal testis [3], simply reducing the size of seminiferous tubules or the number of germ cells [4], streaks gonads [5], a dysgenetic testis and the other streak gonad defining mixed gonadal dysgenesis (as originally proposed by Sohval in 1963 [6]), two dysgenetic testis defining partial gonadal dysgenesis [7], or more rarely coexistence of testicular tissue (seminiferous) and ovarian tissue (stroma with follicles) leading to ovotestis diagnosis [5]. For patients with 45,X/46,XY karyotype, medical care includes not only problems of ambiguous phenotypes caused by the choice of gender, prophylactic gonadectomy or genitoplasty, but also problems related to Turner syndrome resulting from the presence of 45X cell population.

2. Patients and methods

We report five cases of patients with mosaic 45, X/46, XY collected at the Pediatric Endocrinology unit of the Avicenne hospital in Rabat on a period from 2000 to 2010. We analyzed the clinical, hormonal, sonographic, and genitographics data, as well as peroperative and histological findings of these patients.

3. Results

The results of the observations are shown in Table 1.

4. Discussion

The mosaic 45,X/46,XY may be due to a structural abnormality of the Y chromosome, that is predisposing either to late anaphase migration during the first mitotic division resulting directly in a mosaic 45,X/46,XY or to the mitotic no disjunction with formation of three cell lines XO, XY, XXY and subsequent loss of the XYY line [8,9]. The phenotypic consequences of mosaicism 45X/46XY does not seem to be related to the proportion of two cell populations as it was originally proposed [10]. Mosaicism found in lymphocytes (karyotype of the patient), or the amniotic cells (amniocentesis) does not reflect the proportion of gonadal mosaicism and is not correlated to clinical phenotype [1]. It does not seem also that there is a match between gonadal karyotype and the gonad differentiation degree, the theory suggesting that gonadal sex determination in the mosaics is consistent with the predominance of cell population contained in a given gonad has not been confirmed [10]. Pierre et al. [11] proposed another theory, which suggests that the distribution of the X0 and XY cell populations that existed at the critical testicular differentiation has disappeared thereafter, or that the level of mosaicism may be still present in the body, but is difficult to detect. The mosaic 45X/46XY most often leads to a mixed gonadal dysgenesis (MGD) [9,11], this was the case for four of our patients, no similar case in their family was noted. However, as previously stated, other histological situations are possible [5,7], so the mosaic karyotype is not a necessary condition for the occurrence of MGD. The description of familial cases [12], and the presence of patients with XY karyotype without MGD Mosaic [5,7] suggests that it is an entity of heterogeneous etiology, failure of testicular development could be underpinned by determination errors or postzygotic testicular differentiation, but studies in this direction have not been able to determine the existence of mutations in the SRY gene that may explain this heterogeneity [7,10]. Mizuno et al. [13] analyzed the SRY sequence in gonadal for five patients with MGD and noted its absence at the streak gonad of two patients, although it was positive both in the karyotyping blood and in testicular skin cells. Thus, the SRY gene is the point of initiating a complex cascade of molecular events involving opposing forces and crucial alliances before reaching the gonadal sex determination. Several mutations in other genes (PAX2, EMX2, Lhx9, WT1, GATA4, SOX9, SF1, DAX1, etc.) as well as duplication of the dosage sensitive sex (DSS) have been described in cases of gonadal dysgenesis, but the testicular dysfunction was always accompanied by other abnormalities [5]. If the molecular mechanisms are still unclear, one thing is certain, the phenotype is the result of the degree of testicular function, its ability to masculinizing the external genitalia and to regress Mullerian ducts. The discovery of SRY was promising. Since then, and despite more than 20 years of work, few data about this gene are known. The fact that SRY is on the Y chromosome makes it vulnerable to degradation, therefore it is not very well conserved and shows some functional gaps. This is surprising for a gene from which the specie continuity is so dependent [5]. Indeed, some microdeletions of the Y may be accompanied by a high mitotic instability, promote its loss before the period of embryonic gonad differentiation and lead to the formation of mosaic [14,15]. It is therefore necessary before proposing medically assisted reproduction to infertile men to identify these anomalies and to measure the risk [16]. It is well known that the MGD can put them at risk of developing gonadoblastoma, seminoma and of dysgerminoma [3]. This risk is estimated at one third of cases [10], it is maximum around puberty [2]. But the choice of ablation of the gonads is not always easy, if the female is better suited to this state of castration, in males, the risk of degeneration must be balanced against the functional capacity of the gonad, and the psychological impact of gonadectomy. In our two patients assigned to the female (n° 4 and n° 5), gonadectomy was immediately performed by laparoscopy. In patient n° 1 Fig. 1 and 2 the right gonad is normally in place, we kept it based on the data suggesting that no cases of tumor have been reported in normally descended testes [17]. In patient n° 2, the streak gonad was resected, the contralateral gonad preserved and lowered, subject to constant monitoring. Its biopsy didn’t reveal any signs of malignancy. Few studies have examined the long-term intra-abdominal gonads lowered [18]. There is no consensus dictating the best attitude to take. Some authors prefer gonadal biopsy, others argue for prophylactic gonadectomy.
Table 1
Summary of the five observations.

<table>
<thead>
<tr>
<th>Observation</th>
<th>n° 1</th>
<th>n° 2</th>
<th>n° 3</th>
<th>n° 4</th>
<th>n° 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14 months</td>
<td>10 years</td>
<td>7 years</td>
<td>3 years</td>
<td>12 years</td>
</tr>
<tr>
<td>Sex assignment</td>
<td>Male</td>
<td>Male</td>
<td>Male</td>
<td>female</td>
<td>Female</td>
</tr>
<tr>
<td>Size</td>
<td>−2DS</td>
<td>−2DS</td>
<td>Normal</td>
<td>−4DS</td>
<td>&gt; −4DS</td>
</tr>
<tr>
<td><strong>external genitalia:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glans(cm)</td>
<td>2/1</td>
<td>4/2</td>
<td>2/1,5</td>
<td>2.5/1</td>
<td>1.5/1</td>
</tr>
<tr>
<td>Labio-scrotal swelling</td>
<td>Asymmetric</td>
<td>Scrotal</td>
<td>Intermediate</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Orifices</td>
<td>Vulvar</td>
<td>Hypospadias meatus</td>
<td>Posterior hypospadias</td>
<td>Vulviforme hypospadias</td>
<td>Female</td>
</tr>
<tr>
<td>Gonads</td>
<td>Right palpatd</td>
<td>Cryptorchid</td>
<td>Cryptorchid</td>
<td>Not palpated</td>
<td>Not palpated</td>
</tr>
<tr>
<td>Karyotype</td>
<td>45X/46XY</td>
<td>45X/46XY(ring Y)</td>
<td>45X/46XY</td>
<td>45X/46XY</td>
<td>45X/46XY</td>
</tr>
<tr>
<td>Testosterone after HCG</td>
<td>&lt;0,1 ng/mL, 2,8 ng/mL</td>
<td>0,14 ng/mL, 0,36 ng/mL</td>
<td>&lt;0,1 ng/mL, 0,56 ng/mL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Contralateral gonad and Mullerian ducts not visualized</td>
<td>Gonads and Mullerian ducts not visualized</td>
<td>Uterus + vagina</td>
<td>Ovaries not visualized</td>
<td>Prepubertal uterus ovaries and fallopian not visualized</td>
</tr>
<tr>
<td>Génitography</td>
<td>Male urethra + picture addition to suspect Mullerian ducts</td>
<td>Vaginal cavity + uterine cavity + fallopian tubes</td>
<td>Vaginal cavity uterine cavity</td>
<td>Vaginal cavity uterine cavity</td>
<td>–</td>
</tr>
<tr>
<td>Laparoscopy</td>
<td>Hemiutérus + gonad hypoplastic left</td>
<td>Rudimentary uterus 2 fallopian Right gonad Vaginal canal</td>
<td>–</td>
<td>Rudimentary uterus reduced Gonads</td>
<td>Reduced uterus reduced Gonads</td>
</tr>
<tr>
<td>Treatment</td>
<td>Hypospadias surgery attaching the right gonad and left gonad</td>
<td>Hypospadias surgery removal of Mullerian ducts Gonads placed above the inguinal (pedicle short)</td>
<td>–</td>
<td>Bilateral gonadectomy Vaginoplasty Chitioridoplasty</td>
<td>Bilateral gonadectomy</td>
</tr>
<tr>
<td>Histology</td>
<td>Streak gonad + Dysgenetic testis</td>
<td>Streak gonad + Dysgenetic testis</td>
<td>–</td>
<td>Streak gonad + Dysgenetic testis</td>
<td>Streak gonad + Dysgenetic testis</td>
</tr>
<tr>
<td>Diagnosis retained</td>
<td>MGD</td>
<td>MGD</td>
<td>–</td>
<td>MGD</td>
<td>MGD</td>
</tr>
</tbody>
</table>

MGD: Mixed gonadal dysgenesis.

at puberty [2]. Risk assessment of degeneration could be done through PCR research of the gene TSPY (Testis Specific Protein Y-encoded). This gene is linked to the development of gonadoblastoma, seminoma and the other tumors [15]. Recently, another gene involved in the genesis of gonadoblastoma has been...
Hypertrophie clitoridienne de 1,5 cm avec deux orifices urétral et vaginal.

OCT 3/4 [18]. Explorations such as non-invasive ultrasound and testicular tumor markers are always recommended. Given the key role of sex steroids in the acquisition and maintenance of bone mass, the potential impact on bone metabolism of congenital hypogonadotropic led to different studies. These diseases are rare; the consequences of bone gonadal dysgenesis were studied mainly in the two most common types, including Turner syndrome and Klinefelter syndrome. Regarding other etiologies, in this case the MGD, we know no studies that have been published on this subject. If we know that in Turner, there is bone loss associated with a hyper remodelling, that seems to be correlated with hormonal status, what about the other phenotypes karyotype 45X/46XY? Any ways, the predominant factor in the genesis of bone loss is the lack of sex steroids and not the chromosomal abnormality [19], thus an assessment of bone mineral density seems to be needed for patients 45, X/46, XY, all phenotypes combined. On the pubertal, no cases of spontaneous puberty or pregnancy have been reported in women with MGD 45, X/46, XY [5], moreover, because of the presence of Y material, gonadectomy is most frequently performed at a very young age. For men, if spontaneous puberty is possible sometimes, infertility appears in most of the cases however later. [16]. In our series, puberty will artificially be induced in both females (n°4, n°5) and males by a natural estrogen dose-escalation, and in combination with progesterin two years after. In patients without uterus the addition of progesterin is unnecessary [18]. Sex assignment in the MGD is still debatable. For patients 1, 2, and 3 assigned to the male, we have no long-term monitoring to judge their future puberty. Patient n°2 has satisfactory degree of masculinization of external genitalia that may be consistent with the choice of males. But in case 3, the low degree of masculinisation, and the lack of response from the glans at HCG test, may challenge the award of the male in his case. In the David et al. serie [20], which had included 15 patients with MGD, the sex male choice was done for six patients. This approach has been regretted in most of them due to the small size, the iterative genitoplasty and the poor performance of pubertal testosterone function. This brings us back to the difficulties observed with the ambiguous phenotypes related to delayed diagnosis in our context. The average age of diagnosis in our series is 6.6 years and the sex of assignment is usually assigned by parents and not by the medical profession, thus our attitude is limited to genitoplasty consistent with the original sex assigned, because it would be fastidious to go back on sex selection, knowing the psychological impact that might have this kind of decision, both on parents and the child who was already building a sexual identity. Concerning growth, four of our patients had a deficit stature; in girls (case n°4 and n°5) the delay was estimated at less than or equal to 4DS, less severe in boys – 2DS (case n°1 and n°2), case n°3 had a normal size for her age and gender. We have treated with growth hormone cases n°4 and n°5. The small size is generally better tolerated in girls, with unquestionable benefit of treatment with growth hormone [20]. If the karyotype is systematically applied to small girls, it’s not the same for boys. According to the review of amniocentesis, the percentage of male phenotype with apparently normal karyotypes 45, X/46, XY is estimated at 90% [1], the small size, however, is common for these patients. This leads some authors to include it among the exams exploration of short stature for boys, the goal is to enable an early diagnosis for better prognosis for final height after treatment [21]. However, we think it would be more logical to apply it only to cryptorchidism, hypospadias, micropenis, and obviously to cases of Turner syndrome stigmata. Finally, we must emphasize that the management of patients with mosaicism 45, X/46, XY, should also include diagnosis and monitoring of the manifestations of Turner syndrome, especially cardiac anomalies that can be life-threatening.

5. Conclusion

There are rare forms of gonosomal abnormalities whose management requires a multidisciplinary team involving pediatric, endocrinologist, surgeon and psychologist. Indeed, in the ambiguous phenotypes, the decision regarding the assignment of sex must be taken as soon as possible. The occurrence of such a situation is difficult for parents, how it is experienced depends on personal and cultural factors, it can affect how the child is invested by his parents and therefore affect his psychological development. Only an extended follow-up of cases of mosaicism 45, X/46,XY diagnosed prenatally, can help to better assess their long-term outcome on the quality of life, the risk of degeneration, the bone capital, growth, pubertal development, sexual dysfunction, fertility, mental health, self-esteem and relationship skills.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
References