Clinical case

Ascending aortic aneurysm in a patient with mixed gonadal dysgenesis

Anévrisme de l’aorte ascendante chez un patient porteur d’une dysgénésie gonadique mixte

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Available online 4 December 2010

Résumé
Les complications cardiovasculaires et endocriniennes, chez les patients mâles ou ambigus porteurs d’un mosaïcisme 45,X/46,XY ne sont que très peu abordée dans la littérature. A contrario, les jeunes filles atteintes d’une maladie de Turner bénéficient d’un suivi cardiologique et endocrinien régulier, conformément aux recommandations actuelles. Nous rapportons le cas d’un patient de phénotype ambigu âgé de 23 ans, porteur d’une dygénésie gonadique mixte 45,X/46,XY, hospitalisé en cardiologie pour prise en charge d’une défaillance cardiaque associée à une bicuspidie aortique et à un anévrisme de l’aorte ascendante. Par l’illustration de ce cas et des quelques autres décrits dans la littérature, cet article pose l’intérêt d’un suivi cardiologique et endocrinien chez les patients mâles ou ambigus porteurs d’un mosaïcisme 45,X/46,XY.

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Mots clés : Dysgénésies gonadiques mixtes ; Anévrisme aortique ; Suivi cardiologique ; Suivi endocrinien

Abstract

Cardiovascular and endocrine complications in male or sexually-ambiguous patients carrying a 45,X/46,XY mosaicism are rarely discussed in the medical literature. However, young female patients with a diagnosis of Turner’s disease usually benefit from regular cardiologic and endocrine follow-up, in accordance with current international guidelines. We report the case of a male patient, aged 23 years, with an ambiguous phenotype known to harbor a mixed gonadic 45,X/46,XY type dysgenesis. The patient was admitted to the cardiology ward for investigation and management of cardiac failure secondary to both a bicuspid aortic valve and ascending aorta aneurysm. This case report, and the few others, which have been previously reported in the literature, emphasizes the importance of cardiologic and endocrine follow-up in male carriers of 45,X/46,XY mosaicism. © 2010 Elsevier Masson SAS. All rights reserved.

Keywords: Mixed gonadal dysgenesis; Aortic aneurysm; Cardiologic follow up; Endocrinial follow-up

1. Introduction

Gonadal dysgenesis is a reproductive system development disorder.

The incidence of mosaicism 45,X/46,XY is rare and generally underestimated, probably because of the normal male phenotype observed in 95% of patients [1].

In 2% of cases, the phenotype is female, e.g. in Turner’s syndrome, and in 3% there is mixed gonadal dysgenesis with ambiguous genitalia that include a pseudovaginal perineoscrotal hypospadias. We describe the case of a patient belonging to the 3% with mixed gonadal dysgenesis.

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There is very little information in the literature about patients harboring this mosaicism with ambiguous genitalia or male phenotype and the association with cardiovascular complications. We found only six cases reported in the literature.

This case report, together with similarities between Turner’s syndrome and mosaicism 45,X/46,XY, clearly illustrates the importance of initializing a similar follow-up for the two entities.

2. Case report

A 23-year-old male patient, with a known background of chromosomal abnormality 45,X/46,XY, presented to the emergency department with complaints of dyspnea and orthopnea on minimal exertion. There was no associated chest pain.
His past medical history was essentially consistent with phenotype ambiguity with gonadal dysgenesis. Ambiguous genitalia with a pseudovaginal perineoscrotal hypospadias was diagnosed at birth and the karyotype subsequently showed 45,X/46,XY mosaicism.

At 1 year of age, the choice of his final sex was made and he underwent reconstructive surgery with an initial uroplasty to correct the urinary canal, followed later with removal of gonads as oncogenic risk is very high if left in situ.

At 10 years, growth hormone was started till age 15 despite the lack of GH deficiency on insulin induced hypoglycemia testing. The decision was made in agreement with the Belgian Group of pediatricians because of 10-year-old height on the 25 percentile, and the known resistance to GH hormone, as in Turner’s syndrome. From the age of 12 years, intramuscular androgen injections were regularly administered. Mental and physical development seemed harmonious and the patient married.

He also developed hypothyroidism secondary to autoimmune thyroiditis, treated with L-thyroxin, and glucose intolerance treated with metformin.

Physical examination showed a patient without physical characteristics of Turner’s syndrome. He was overweight with a body mass index of 26. Blood pressure was normal at 120/80 mmHg and heart rate 80 bpm. There was a systolic ejection murmur at the pulmonary valve region and a grade 2/6 aortic ejection murmur identified at heart auscultation.

The electrocardiogram revealed a sinus rhythm (80 bpm) and left ventricular hypertrophy. The chest X-ray showed features of cardiomegaly with enlarged mediastinum. Echocardiography showed a leaking bicuspid aortic valve, a dilated left ventricle, with severe global hypokinesia and ejection fraction at 15%, a dissecting aortic aneurysm of the ascending part of the thoracic aorta measuring 8 cm in diameter. The dissection involved the beginning of the aortic arch as confirmed on the CT scan.

Further blood investigations showed satisfactory diabetes and thyroid control, with normal TSH at 1.63 microunits/ml (normal range between 0.1 and 3.50), normal glycated hemoglobin at 5.4% (normal range between 4 and 6).

The patient was treated medically and after a few months showed slow recovery of heart function. Cardiac surgery was performed: Bentall procedure, i.e. concomitant aortic valve replacement and ascending aorta repair with a Dacron prosthesis. One year after the procedure, the patient was doing well. At physical examination, blood pressure was normal and there was no heart murmur. Left ventricular ejection fraction improved to 35%.

3. Discussion

Turner’s syndrome is a chromosomic disorder that affects one in 2500 live born females and is characterized by complete or partial loss of one X chromosome. The karyotype can be a monosomy 45,X/45,X, a mosaicism 45,X/46,XX or an anomaly of the X chromosome. In the mosaicism karyotype, the clinical features can be difficult to diagnose. A karyotype should always be requested in girls with short stature and a standard deviation of 2 S.D. [2]. Turner’s syndrome is associated with important cardiovascular complications with an incidence varying from 20 to 40% that includes bicuspid aortic and coarctation of the aorta. These complications are more frequently observed in monosomy [3].

Aortic dissection is however rare. Very few cases have been described in the literature, but this associated abnormality can be seen in patients without any previous cardiovascular malformations. The risk factors leading to these complications are hypertension found in 50% of patients with Turner’s disease [4], hyperlipidemia and glucose intolerance or diabetes [5].

Guidelines suggest that all Turner’s patients should have ultrasonic monitoring at different stages of their life: at diagnosis, onset of adult life, and then every 5 years if there are no risk factors.

In case of associated risk factors (hypertension, bicuspid aortic valve, coarctation of the aorta), a yearly ultrasound or MRI is advised [6].

Endocrine follow-up consists in monitoring fasting glucose every 2 years and when starting hormonal treatment by growth factor and also monitoring thyroid function including auto antibodies from the age of 4 years.

Per guideline follow-up is advisable for all patients with Turner’s syndrome including those 2% with karyotype 45,X/46,XY and a Turner’s female phenotype.

Ninety-five percent of patients with karyotype 45,X/46,XY presents a normal male phenotype at birth. Their follow-up shows a high incidence of short stature for which growth hormone injections are beneficial [7].

Many authors propose a karyotype analysis for all male patients with a short stature, height situated below – 2 S.D. as done for [8] patients with Turner’s syndrome.

Some patients with normal male phenotype at birth have turned out to have Turner’s stigmata [9]. Our patient presented with short stature treated with growth hormone, thyroiditis and glucose intolerance that are also seen with Turner’s syndrome.

The literature relates only six cases of cardiovascular malformations in patients with karyotype 45,X/46,XY with male or ambiguous phenotype (Table 1).

Among these cases described in the literature, the striking one is described by Fujimoto. He reported the case of twins with monozygotic 45,X/46,XY with identical chromosome Y.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cardiovascular malformations in patients with karyotype 45,X/46,XY. Malformations cardiovasculaires chez les patients porteurs d’un karyotype 45,X/46,XY.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al. (1990) [1]</td>
<td>92 patients</td>
</tr>
<tr>
<td>Büyübeziz and Oren (1993) [10]</td>
<td>2 cases of cardiovascular malformations</td>
</tr>
<tr>
<td>Willis et al. [12]</td>
<td>4-year-old child with penial hypospadias and coarctation of the aorta</td>
</tr>
<tr>
<td>Fujimoto et al. [13]</td>
<td>15 patients, one case of cardiovascular malformation</td>
</tr>
<tr>
<td>Muntaz et al. [14]</td>
<td>2 homozygous twins, one baby with female Turner phenotype and coarctation of the aorta and the other with normal male phenotype</td>
</tr>
</tbody>
</table>

Hypoplastic left heart and severe aortic stenosis.
One of the twins had normal male phenotype and the other had female phenotype associated with coarctation of the aorta. According to the current recommendations, the baby with male phenotype would not require cardiology follow-up. These different cases highlight similarities between patients with karyotype 45,X/46,XY and Turner’s syndrome.

Therefore, we believe that all patients with a diagnosis of mosaicism 45,X/46,XY associated with ambiguous genitalia, hypospadias or short stature should be proposed for cardiology and endocrine follow-up as for Turner’s syndrome patients.

4. Conclusion

This text describes the complexity in the management of a patient with chromosomal abnormality 45,X/46,XY. This complexity is heightened by the lack of clear guidelines for cardiologic and endocrine follow-up of this cohort of patients. For these patients, we strongly advocate follow-up similar to that generally proposed for patients with confirmed Turner’s syndrome.

Conflict of interest statement

There is no interest’s conflict.

References