Descriptive analyses of Turner syndrome: 49 cases in Tunisia

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Abstract

Turner syndrome is linked to the absence or abnormality of one of the X chromosome leading to haplo-insufficiency of genes involved in the development and maintenance of the ovarian stock in women. We report the results of a 21-year retrospective study, conducted in 49 patients with Turner syndrome. The purpose of this study was to establish the clinical, hormonal, cytogenetic and evolutive pattern of a Tunisian population with Turner syndrome and to search for correlations between genotype and phenotype. The average age of our patients at diagnosis was 14 years (1 day–42 years). Twenty-four percent of them were diagnosed in adulthood (greater or equal to 20 years). Turner syndrome was diagnosed later in the case of mosaicism ($P = 0.001$). Short stature was present in 85% of cases; it was more frequent among the youngest and monosomics. The dystrophic syndrome was observed in 85% of cases; it was significantly more frequent in monosomics ($P = 0.003$). Delayed pubertet was present in 62.4% of cases; it was almost constant in monosomics ($P = 0.05$). The loss of ovarian function was more severe in case of monosomia compared to other forms ($P = 0.04$). Our results report a high frequency of autoimmune diseases (18/46 cases) including dysthyroidism (eight cases). Hepatobiliary affections were more frequent in mosaicism compared to monosomy. The average final height was greater even in mosaicism estimated at 150.5 cm compared to 141 cm in monosomics and 138.8 cm in mosaics with abnormal structures.

Keywords: Turner syndrome; Short stature; Dysmorphic syndrome; Delayed puberty

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1. Introduction

Turner syndrome (TS) is a chronic disease related to the absence or abnormality of one of the two X chromosomes causing haplo-insufficiency of genes involved in the development and maintenance of ovaries capital in a patient with female phenotype [1]. TS occurs in about 1/2500 to 1/5000 female births [2]. The phenotype is the result of haplo-insufficiency of the gene on the X chromosome that prevents premature inactivation of the X chromosome during the embryogenesis process [3]. Furthermore, this syndrome may involve various visceral malformations especially in the heart and the kidneys with a variable frequency related mainly to the type of chromosomal deletion (monosomy or mosaicism).

The purpose of this study is to determine the clinical, hormonal, cytogenetic and the evolving characteristics of Tunisian female patients with TS and to search for correlations between genotype and phenotype.

2. Patients and methods

This retrospective multicenter study was conducted in 49 patients seen over a period of 21 years, from 1987 to 2008 in the Endocrinology and Pediatric wards in Sfax and the Pediatrics ward in Monastir (Tunisia). The cytogenetic study was based on cell culture using standard technique [2]. An analysis of at least 15 mitoses was made for all patients. We divided our population into three groups according to the chromosome formula. We found 29 cases of monosomy, 12 cases of mosaic without structural abnormalities and eight cases of anomalies with mosaic structures (Table 1). We also studied the various complications of this syndrome:

- cardiovascular complications were detected by physical examination and confirmed by echocardiography. This exam was performed in 16 patients. Renal complications were detected by renal ultrasound performed in 37 patients;
- hypothyroidism and other autoimmune diseases were screened by physical exam and biological assessment;
- the impaired glucose tolerance was systematically analysed by fasting plasma glucose test;
- hepatobiliary disorders and dyslipidemia were detected on the basis of blood tests performed in 28 and 27 patients respectively.

SPSS 11.5 was used to search for correlations between phenotype and genotype. The cohort was also assessed in adulthood.

3. Results

3.1. Age

The average age of our patients at the time of diagnosis was 14 years (1 day–42 years). In the majority; diagnosis was established between the ages of 10 and 20 years. Twenty-four percent of our patients were diagnosed in adulthood (greater or equal to 20 years) (Fig. 1). Turner syndrome was diagnosed at a late stage in case of mosaicism. Indeed the average age of monosomics was 18.4 years versus 24.5 years for mosaics without structural abnormalities and 21.3 years for anomalies with mosaic structures ($P = 0.01$) (Fig. 2).

Familial Turner syndrome was reported in one family with three TS in sisters. These patients were aged respectively 31, 17 and 13 years. They were born to consanguineous parents. The cytogenetic study showed a homogeneous monosomy 45 XO in

Table 1

<table>
<thead>
<tr>
<th>Chromosome formula</th>
<th>Number of cases</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy 45 XO</td>
<td>29</td>
<td>58.5</td>
</tr>
<tr>
<td>Mosaicism without structural anomalies</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>45X/46XX</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>45X/46XX/47XXX</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>45X/46XX/49XXXXX</td>
<td>1</td>
<td>2.1</td>
</tr>
<tr>
<td>45X/46XY</td>
<td>2</td>
<td>4.3</td>
</tr>
<tr>
<td>Mosaicism with structural anomalies</td>
<td>8</td>
<td>17.3</td>
</tr>
<tr>
<td>46 Xi (Xq)/45</td>
<td>5</td>
<td>10.8</td>
</tr>
<tr>
<td>46 Xi (Xp)/46XX</td>
<td>3</td>
<td>6.5</td>
</tr>
<tr>
<td>Mosaicism with Y chromosome</td>
<td>1</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Fig. 1. Age range of our patients.

Répartition de nos patientes selon les tranches d’âge.

Fig. 2. Correlation between age and chromosome formula.

Corrélation tranche d’âge/caryotype.
3.2. Consanguinity

Parental consanguinity was found in more than half of the cases (60%).

3.3. Short Stature

Growth failure was present in 85% of cases. A positive correlation between the height of the patients and their parents was observed ($P = 0.05$). Short stature was more frequent among young patients but no correlation with the karyotype was noted. Short stature was particularly common in monosomic patients (23 cases compared with six cases in mosaicism without structural abnormalities and 10 cases among the mosaic patients with abnormal structures) (Fig. 3).

Results of the cytogenetic study and the distribution by chromosome formula are given in Table 1.

3.4. Dysmorphic syndrome

A dysmorphic syndrome was found in the majority of patients (85%). It was significantly more frequent in cases of monosomy than in mosaicism with or without structural abnormalities ($P = 0.003$) (Fig. 4) Dysmorphic syndrome was also more common in younger patients whatever the karyotype but not significantly.

3.5. Pubertal development

Delayed puberty was present in 62.4% of cases. The delayed puberty was an almost constant sign in monosomy (15/20 monosomy at the age of puberty) with a significant difference ($P = 0.05$). Spontaneous puberty was more common in patients with mosaicism with or without abnormal structures, but no significant difference between the three groups ($P = 0.2$) was noted (Table 2 and Fig. 5). The average serum FSH was 82.5 mU/ml (1–180), and 18.6 mU/ml (0.19–41) for LH.

3.6. Ultrasound data

The ovarian damage was more severe in monosomies than the other chromosomal forms ($P = 0.04$) (Fig. 6 and Table 3). Urinary anomalies and/or heart disease were more frequent in monosomies and mosaicism without abnormal structures while

Table 2

<table>
<thead>
<tr>
<th>Pubertal disorders.</th>
<th>Number</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbuerism</td>
<td>19</td>
<td>55.8</td>
</tr>
<tr>
<td>Delayed puberty</td>
<td>10</td>
<td>29.4</td>
</tr>
<tr>
<td>Primary amenorrhea</td>
<td>25</td>
<td>81</td>
</tr>
<tr>
<td>Secondary amenorrhea</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Spaniomenorrhea</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Spontaneous secondary sexual character</td>
<td>5</td>
<td>14.7</td>
</tr>
<tr>
<td>Spontaneous menarche</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

Fig. 4. Frequency of dysmorphic syndrome according to chromosome formula. Fréquence du syndrome dysmorphe en fonction de la formule chromosomique.

Fig. 5. Repartition of pubertal anomalies according to chromosome formula. Répartition des anomalies pubertaires selon la formule chromosomique.
they were nearly absent in cases of abnormal structures, but with no significant difference ($P = 0.09$). These malformations were more common in young people.

3.7. Hepatobiliary disorders

Hepatobiliary disorders were detected by biological tests. We noted a hepatic cytolyis in 7/28 cases (25%) and cholestatic liver in 10/24 cases. It was more common in cases of mosaicism than in monosomy.

3.8. Autoimmunity

Our results indicated a high incidence of autoimmune diseases associated with Turner syndrome 39.1% (18/46) including thyroid dysfunction in eight cases (15%). These diseases were more frequent in monosomies ($P = 0.1$) and in young patients (Table 4).

3.9. Treatment of growth failure and delayed puberty

Treatment with growth hormone (GH) was prescribed for seven patients (27%) of patients at the age to be treated. The dose was 0.9 to 1 IU/kg/week. This treatment was started at an average chronological age of 11 years (8.5 to 14 years), an average bone age of 9 years (7 to 10 years) with a mean duration of 2 years (0.5–5 years). The mean statural gain was 13.5 cm (1 to 25 cm) with an average final height of 135 cm (122 to 148). The statural gain was greater if the age at onset was younger.

Hormone replacement therapy was prescribed for 13 patients with completion of puberty after 2 years of treatment.

4. Discussion

Compared to the literature findings, our study reports a higher rate of homogeneous monosomies. Indeed various studies show a rate of monosomy ranging between 36.6 and 45% [4–7] and a rate of mosaicism without structural abnormalities varying between 33 and 41% [3–8]. Several studies show an earlier age on diagnosis in case of monosomy. Sybeert et al. [9] showed that 25% of mosaic patients were diagnosed in adulthood. Short stature is associated with haplo-insufficiency of the SHOX gene located in the pseudo autosomal region of the X (Xp11-22) [4–23] and Y (YP 11). It is often a diagnosing circumstance for Turner syndrome.

Table 4

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid disorders</td>
<td>8 cases (15)</td>
</tr>
<tr>
<td>Hashimoto disease</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>Basedow disease</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>Goiter</td>
<td>4/8 (50)</td>
</tr>
<tr>
<td>Auto immune disease</td>
<td>10 cases (22)</td>
</tr>
<tr>
<td>Poly rheumatoid arthritis</td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>2/10 (20)</td>
</tr>
<tr>
<td>Disorder of glucid tolerance</td>
<td>13 cases (28.2)</td>
</tr>
<tr>
<td>Heart anomaly (stenosis of PA, AI, coartation of the aorta, aortic stenosis)</td>
<td>8/16 (5)</td>
</tr>
</tbody>
</table>

3.10. Evaluation in adulthood

The evolution of TS in adulthood was studied in 24 patients. The spontaneous final height, measured in patients not treated with GH, averaged 143.7 cm (127–165). The spontaneous final height was higher in cases of mosaicism without structural abnormalities (150.5 cm) versus (141 cm) in monosomy and (138.8 cm) in mosaicism with abnormal structures. Metabolic disorders were present only in monosomies and mosaicism without structural abnormalities. The average body mass index (BMI) of our adult patients was 20.9 kg/m² (15–30). Three patients (12%) were overweight; one patient was obese with a BMI at 30 kg/m². Dyslipidemia was observed in six patients (25%) and four patients (16%) suffered from type 2 diabetes. Hypertension was noted in two patients (8%). Psycho-affective disturbances were noted in two patients (8%). There was also a higher incidence of impaired learning abilities among monosomies (6/29; 20.9%). Three patients had a normal life; three out of 24 patients had a normal sexual life. One patient died of acute heart failure at the age of 14.
of TS with a rate of 54% in our study which seems higher than that of Virginia et al. who reported that 1/3 of patients with TS are diagnosed in childhood and are revealed by short stature (RS) [5]. Our results are consistent with those of Elsheikh et al. who reported a higher frequency of short stature (RS) in monosomy and mosaicism with abnormal structures. These results are due to the loss of one allele of the gene SHOX [2–5,8]. Gonadal dysgenesis is due to the haplo-insufficiency of genes involved in ovarian maintenance located on the long arm of the X chromosome, Xq26 (POF1) and Xq 13-21 (POF2) [11]. In contrast, a deletion of the distal short arm is compatible with a normal ovarian function [12–15]. In literature, spontaneous puberty is seen in 2–5% [13], which fits the data of our series.

Both the stature study conducted on 704 patients and the Italian multicenter study conducted on 522 patients show spontaneous puberty occurs in 9.8% and 16.1% respectively [14]. The presence of spontaneous puberty was more frequent in mosaicism with or without structural abnormalities compared to monosomies and this point was confirmed by several studies [15]. In fact only 14% of monosomies versus 32% of mosaic patients, with a second X chromosome, show signs of puberty [17]. Sybert et al. [16] showed in 10 cases of TS, that 8/10 girls have follicles in their ovaries, and that the follicular density of ovarian cortex is greater in mosaicism. The presence of chromosome Y that predicts a high risk of gonadoblastoma is reported in 6.4% in our study, which is concordant with the literature result (6.2%) [3].

Renal malformations are nine times more frequent among patients with TS than in the general population [17]. Different studies report a rate of renal malformations from 25 to 43% which exceeds the rate reported by our study, which is probably due to the lack of systematic renal ultrasound examination [18–29].

Congenital heart diseases are noted in 17 to 45% of patients [10], which agrees with our results (50%). Autoimmune thyroiditis is especially diagnosed at an early age with a peak at 4 years [21], which was confirmed in our study. Livadas et al. reported a thyroid dysfunction in 24% of 84 patients aged between 0 to 19 years [21].

Apart from treatment with GH, Elsheikh et al. reported a spontaneous final height at 143 to 147 cm in Caucasian patients [20], which joins our results. Obesity is a common problem in the TS [25]. The etiology of obesity is so far unexplained but several studies have addressed the role of estrogen deficiency [31]. It was also shown that hormone replacement therapy decreases fat mass and the ratio TT/TH in these patients but without changing BMI [26,27]. Type 2 diabetes is twice to four times as common among TS patients than in the general population [28,29]. Thus the frequency of carbohydrate disorders reported in the literature varies from 10 to 34% [30,31], which was also found in our study. In a recent study of 28 women the rate of dyslipidemia was 50% [20]. Several studies report a beneficial effect of GH therapy on lipid metabolism with lowering LDL-C and increasing HDL-c [32]. Murphy et al. [20–33] have shown that women with 45X0 had a significantly lower performance score compared with patients who had a mosaic. Preservation of the activity of the ring chromosome is responsible for mental retardation; in consequence the inactivated X ring is associated with normal intelligence [24]. In the literature, the frequency of patients who reach a higher level of schooling varies from 19 to 33% [20]. Our findings corroborate with some data from the literature as 12% of the patients attended the university. A Danish study reported an average age at death at 65 years from cardiovascular diseases in 50% [34,35]. The only death in our data was a 14-year-old girl in a setting of acute cardiac failure. Schoemakher et al. report that mortality in Turner’s syndrome is three times higher than in the general population [6].

5. Conclusion

Turner syndrome is a genetic syndrome most frequently characterised by short stature, dysmorphic syndrome and gonadal failure. These are the main problems a multidisciplinary team monitors and manages during childhood. Endocrinologists should focus on the different aspects of this syndrome in order to ensure adequate care of these patients.

6. French version

A french version of this article is available at doi: 10.1016/j.ando.2009.1.013.

Conflict of Interest

The authors have not declared any conflict of interest.

References


