CORRELATION BETWEEN THE DEGREE OF MENTAL RETARDATION AND THE PRESENCE OF RING X CHROMOSOME IN TURNER SYNDROME PATIENTS - REPORT OF 4 CASES

Introduction

Turner syndrome is defined as a chromosomal disease, caused by the numerical or structural aberration of one of the two X chromosomes, which affects one out of 2000 newborn babies. Clinically, it is characterized by growth deficits, gonadal dysgenesis, evidenced by genital infantilism, primary amenorrhea, infertility, heart and kidney abnormalities, as well as characteristic stigma. X monosomy or the lack of a fragment of the X chromosome is not necessarily associated with mental retardation, over 90 percent of the Turner patients have normal intellectual functions, 55% of them have the following karyotype: 45, X; 20 % have isochromosome Xq, 10% have been diagnosed with a mosaic karyotype 45, X/46, XX, while other 10% have a mosaic karyotype of 45, X with a second cellular line having an X chromosome with a structural anomaly.

The first two cases with 45,X/46,X,r(X) and mental retardation were reported in 1987 by Kushnick et al.(1). In 1990 J.P.Fryns et al. (2) published a study that included 21 patients, 6 of them having ring X chromosomes. Nielsen (3) communicates 2 cases of severe mental retardation in patients with Turner syndrome and mosaic karyotypes 45, X/46X, r(X). Fisher and Naslung (4), de Almeida et al.(5) have described a Turner syndrome case with severe mental retardation (I.Q.=31). The cytogenetic analysis has shown the presence of a small fragment whose origin out of the X chromosome has not been demonstrated. Bieder (6) and Bender (7), Crolla and Llerena (8) have reported cases of patients with ring X chromosome with borderline intelligence or mild mental retardation.

Summary:

In this report we present 4 cases of Turner syndrome patients with ring X chromosome. A high incidence of mental retardation of different degrees in Turner syndrome patients with ring X chromosome was reported. The degree of mental retardation varies from borderline intelligence to severe mental retardation.

Key words: mental retardation, ring X chromosome, Turner syndrome.

REZUMAT

In aceasta lucrare prezentam 4 cazuri de sindrom Turner cu cromozom X in ring. In literatura a fost raportata o incidenata crescuta a retardului mental la pacientii cu sindrom Turner si cromozom X in ring. Gradul retardului mental variaza de la inteligenta de granita pana la retard mental sever.

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A special attention has been granted to XIST gene that plays an essential role in the initiation of X inactivation (Borsani et al.,9). Migeon (10) was the first who detected the absence of XIST transcription from small r(X) chromosomes in patients with sever phenotypes. Wolf et al.,(11) reported five patients with XIST negative r(X) chromosomes.

24 cases with Turner syndrome have been investigated between 2000-2006, within the Genetics Laboratory of the Medical Genetics Department of UMF Timisoara, 4 of which exhibited Turner syndrome with the ring X chromosome. The purpose of this research paper is to report the intellectual as well as physical development of these 4 cases.

Methods and materials

Out of 315 couples who showed up in the Genetics Laboratory for reproductive failures, 24 women presented Turner syndrome. Out of these 24 cases, 4 patients had the ring X chromosome: 3 female (P.A., M.D. and B.V.) presented mosaic karyotypes 45, X/46, X, r(X), while the remaining one, M.A. had 45, X/46, X, r(X)/46, XX .(Fig.1)

The cytogenetic analysis was performed from the peripheral blood lymphocytes using the standard culture technique, followed by the GTG banding. FISH technique and screening for low level Y mosaicism by PCR of the SRY region (sex determining region Y) were carried out. The potential increased risk of gonadoblastoma in Turner syndrome patients carrying the Y chromosome sequences justifies the application of FISH and PCR methods for the detection of low level Y mosaicsisms when Y chromosome material is not detected by standard cytogenetic analysis in patients with a 45,X karyotype. CEP X probes were used for the FISH analysis.(Fig. 2)

Fig.1 Giemsa banded karyotype of M.A. patient illustrating one X chromosome and a ring X chromosome

Fig. 2 FISH on metaphases from the patient M.D. showing the normal X chromosome and the ring X chromosome
Special attention has been granted to the intellectual development of the patients. 2 of them had normal intellect, they graduated school and currently are working. Another patient showed moderate mental retardation, while the fourth had severe mental retardation.

The phenotypes of the 4 investigated cases are presented in table 1:

The dysmorphies and the IQ of these 4 patients are presented in table 2:

Table 1 The phenotypes in Turner syndrome

<table>
<thead>
<tr>
<th>CASE</th>
<th>AGE</th>
<th>HEIGHT</th>
<th>MENSTRUATION</th>
<th>HAIRNESS</th>
<th>THORACIC</th>
<th>TANNER SCALE</th>
<th>FINGERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.A.</td>
<td>49</td>
<td>141 cm</td>
<td>Amenorrhea</td>
<td>absent</td>
<td>widen</td>
<td>I</td>
<td>brachydactily</td>
</tr>
<tr>
<td>P.A.</td>
<td>20</td>
<td>152 cm</td>
<td>amenorrhea</td>
<td>Reduce in pubis, absent axial</td>
<td>widen</td>
<td>II</td>
<td>brachydactily, hypoplastic finger IV</td>
</tr>
<tr>
<td>M.D.</td>
<td>18</td>
<td>133 cm</td>
<td>amenorrhea</td>
<td>reduce</td>
<td>widen</td>
<td>I</td>
<td>brachydactily</td>
</tr>
<tr>
<td>B.V.</td>
<td>31</td>
<td>160 cm</td>
<td>present</td>
<td>reduce</td>
<td>widen</td>
<td>II</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 The dysmorphies in Turner syndrome

<table>
<thead>
<tr>
<th>CASE</th>
<th>PALATE</th>
<th>NECK</th>
<th>SPEECH</th>
<th>AFFECTIVITY</th>
<th>I.Q.</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.A.</td>
<td>high arched</td>
<td>webbed</td>
<td>incapacity of expression</td>
<td>Nervous, anxious</td>
<td>54</td>
</tr>
<tr>
<td>P.A.</td>
<td>high arched</td>
<td>webbed</td>
<td>normal</td>
<td>normal</td>
<td>95</td>
</tr>
<tr>
<td>M.D.</td>
<td>high arched</td>
<td>webbed</td>
<td>difficulties of pronouncing</td>
<td>immaturity, uncertainty, nervous</td>
<td>38</td>
</tr>
<tr>
<td>B.V.</td>
<td>high arched</td>
<td>webbed</td>
<td>normal</td>
<td>normal</td>
<td>89</td>
</tr>
</tbody>
</table>

Discussions

Out of the 24 Turner syndrome diagnosed patients, 4 had the ring X chromosome. We consider that in this sub-group, mental retardation incidence is high. 50 percent of the patients with Turner syndrome and ring X chromosomes were mentally retarded, 25 percent presented moderate mental retardation and 25 percent severe mental retardation.

Other studies done in order to evaluate the intelligence of the Turner syndrome patients showed that 90 percent of the patients had normal intellect, while 10 percent showed a variable degree of mental retardation. The hypothesis that our patients have been selected for studies is excluded. The cytogenetic analysis was done based on the Turner syndrome suspicion, and not on the mental retardation suspicion.

It is difficult to explain the high incidence of the mental retardation in Turner syndrome patients with ring X chromosome, compared to Turner syndrome patients who present other chromosomes abnormalities. An explanation could be the presence of an inactive X chromosome in some tissues at some time. The researchers consider that mental retardation can be caused by inactivation incapacity of small ring X chromosome, which leads to functional disomy of the X chromosome. This fact is explained by the lack of gene sequence necessary for the inactivation of the X chromosome. Another explanation can be the mosaicism, with the absence of the r(X) chromosomes in some tissues, such as the brain, which is important for the development of the severe phenotype including mental retardation. A ring chromosome is at a high risk of breaking during mitosis and is more unstable than a linear chromosome. When
the ring can not segregate correctly, it can break, lose material and rejoin in a smaller ring or may be lost from the cell.

Conclusions

In the patients of this study, the size of the X chromosome presented large variations, from a patient to another, as well as from a cell to another in the same individual. A comparison between the patients showed: 45, X (70%)/46, X, r(X) (30%)(B.V.), and 45, X (65%)/46, X, r(X) (35%)(P.A.), in those with the ring X chromosome and with normal intellect, while those with mental retardation had 45, X (25%)/46, X, r(X)(75%)(M.D.) and 45, X(10%)/46, X, r(X)(70%)/46, XX(20%)(M.A.). This suggests that a growing percentage of cells with the ring X chromosome have a negative influence over the intellectual development. Given the fact that all analysis have been done out of the lymphocyte of peripheral blood, it is possible that the total percentage of the 45,X cells compared to the 46,X,r(X) cells may not be exact.

In patients with Turner syndrome and mental retardation, the presence of the ring X chromosome may interfere the X inactivation pathway. This could be used as a lead for understanding the mechanism of the X chromosome inactivation.

References