Turner syndrome diagnosed in northeastern Malaysia

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ABSTRACT

Introduction: Turner syndrome affects about one in 2,000 live-born females, and the wide range of somatic features indicates that a number of different X-located genes are responsible for the complete phenotype. This retrospective study highlights the Turner syndrome cases confirmed through cytogenetic analysis at the Human Genome Centre of Universiti Sains Malaysia, from 2001 to 2006.

Methods: Lymphocyte cultures were set up using peripheral blood samples, chromosomes were prepared, G-banded, karyotyped and analysed in accordance to guidelines from the International System for Human Cytogenetic Nomenclature.

Results: The various karyotype patterns observed were 45,X; 46,X,i,(Xq); 45,X/45,X,+mar; 45,X/46,X,i,(Xq) and 45,X/46,XY. The mean age of our patients with Turner syndrome was 21 years, and the most common clinical features encountered in all these patients were short stature (100 percent), primary amenorrhoea (85.7 percent), absence of secondary sexual characteristics (57.1 percent), scanty pubic and axillary hair (50 percent), webbed neck (42.9 percent), wide carrying angle (42.9 percent), rudimentary uterus with bilateral streak ovaries (42.9 percent), underdeveloped breasts (35.7 percent) and wide-spaced nipples (21.4 percent).

Conclusion: Even though there is no causal therapy for Turner syndrome, management and treatment are possible for malformations and conditions associated with it. In addition, counselling of the parents and of the patients themselves are necessary. Hence, establishing an early diagnosis, educating and increasing awareness among doctors, and if possible, a prenatal diagnosis, will help in early intervention, genetic counselling and in improving the quality of life in these patients.

Keywords: cytogenetic analysis, genetic counselling, gonadal dysgenesis, short stature, Turner syndrome

INTRODUCTION

Turner syndrome, gonadal dysgenesis or gonadal agenesis represents a special variant of hypergonadotrophic hypogonadism, and is due to the lack of the second sex chromosome or parts of it. This syndrome affects about one in 2,000 live-born females. The wide range of somatic features in Turner syndrome indicates that a number of different X-located genes are responsible for the complete phenotype. The syndrome includes those individuals with a phenotypic spectrum from female to male, with varying clinical stigmata of the syndrome, as described by Turner. Though many karyotype abnormalities have been described in association with Turner syndrome, monoclonal monosomy X and its various mosaicisms, each with an X monosomic (XO) cell clone, are the most frequent karyotype anomalies. In other instances, the syndrome is due to a structural anomaly of the second X chromosome. The symptoms of this syndrome have been logically deduced to be caused by a single dosage of genes that are normally present and active in two dosages.

METHODS

Peripheral blood was collected from the patients and lymphocyte cultures were set up using RPMI 1640 medium, foetal bovine serum, antibiotics, and phytohaemagglutinin (mitogen). The cultures were incubated at 37°C for 72 hours following which the cell division was arrested by the addition of colcemid. The cultures were then harvested and chromosomes were prepared by the conventional method, following which they were G-banded, karyotyped and analysed according to guidelines from the International System for Human Cytogenetic Nomenclature (ISCN).

Table I. Various karyotype patterns of Turner syndrome.

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>No. of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>45,X</td>
<td>8</td>
</tr>
<tr>
<td>46X,i(Xq)</td>
<td>3</td>
</tr>
<tr>
<td>45,X/45,X,mar</td>
<td>1</td>
</tr>
<tr>
<td>45,X/46,X,i(Xq)</td>
<td>1</td>
</tr>
<tr>
<td>45,X/46,XY</td>
<td>1</td>
</tr>
</tbody>
</table>
In three cases, the sex-determining region–Y (SRY) test was also carried out to confirm the results of the routine cytogenetic analysis. For the SRY test, the DNA was extracted and amplified for the SRY gene using polymerase chain reaction (PCR). The PCR product was then run on gel electrophoresis for the detection of the bands.

RESULTS
The cytogenetic analysis for the Turner syndrome cases showed different patterns of karyotypes (Table I). The mean age of our patients with Turner syndrome was 21 (range 8–47) years. The most common clinical features encountered in all these patients were short stature (100%, 14/14), primary amenorrhoea (85.7%, 12/14), absence of secondary sexual characteristics (57.1%, 8/14), scanty pubic and axillary hair (42.9%, 6/14), webbed neck (42.9%, 6/14), wide carrying angle (42.9%, 6/14), rudimentary uterus with bilateral streak ovaries (42.9%, 6/14), underdeveloped breasts (42.9%, 6/14) and widely-spaced nipples (21.4%, 3/14). A history of slow weight gain, as well as abnormality of the kidney, was observed in one case. Flat feet were present in another case. A third case presented with an overlapping of the fourth toe on the fifth toe bilaterally with osteoporosis of the neck of the femur. Mental retardation was noticed in a single Turner case, and short metacarpal bones were seen in one patient.

Table II. Clinical phenotypes of the 14 Turner patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Short stature</th>
<th>Webbed neck</th>
<th>Widely-spaced nipple</th>
<th>Under-developed breasts</th>
<th>Wide carrying angle</th>
<th>Scanty pubic and axillary hair</th>
<th>Rudimentary uterus with bilateral streak ovaries</th>
<th>Primary amenorrhoea</th>
<th>Absence of secondary sexual characteristics</th>
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<td>2.</td>
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<td>×</td>
<td>×</td>
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<tr>
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<tr>
<td>8.</td>
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<tr>
<td>9.</td>
<td>16</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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</tr>
<tr>
<td>10.</td>
<td>28</td>
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<td>×</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>11.</td>
<td>16</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>✓</td>
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<tr>
<td>14.</td>
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<td>✓</td>
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<td>✓</td>
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</tbody>
</table>

Table III. Mean and standard error (SE) of the different hormonal profiles of the Turner patients.

<table>
<thead>
<tr>
<th>Hormonal test</th>
<th>Mean ± SE</th>
<th>Range</th>
<th>Normal range</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FSH (mIU/ml)</td>
<td>79.79 ± 19.19</td>
<td>34.5–200</td>
<td>25.8–134.8</td>
<td>16–47</td>
</tr>
<tr>
<td>TSH (µIU/L)</td>
<td>2.26 ± 0.59</td>
<td>3.6–13.6</td>
<td>0.5–4.7</td>
<td>16–47</td>
</tr>
<tr>
<td>LH (mIU/L)</td>
<td>27.53 ± 6.04</td>
<td>8.2–72.2</td>
<td>7.7–58.5</td>
<td>16–47</td>
</tr>
<tr>
<td>Progesterone (nmol/L)</td>
<td>1.74 ± 0.26</td>
<td>1.12–2.2</td>
<td>0.3–2.5</td>
<td>16–47</td>
</tr>
<tr>
<td>Testosterone (nmol/L)</td>
<td>11.26 ± 9.14</td>
<td>0.3–52.1</td>
<td>0.2–2.9</td>
<td>16–47</td>
</tr>
<tr>
<td>Free T4 (pmol/L)</td>
<td>14.52 ± 1.41</td>
<td>11.5–19.07</td>
<td>9.1–23.8</td>
<td>16–47</td>
</tr>
<tr>
<td>Prolactin (µIU/ml)</td>
<td>410.32 ± 78.77</td>
<td>169–657.6</td>
<td>102–496</td>
<td>16–47</td>
</tr>
<tr>
<td>Oestradiol (pmol/L)</td>
<td>51.74 ± 18.37</td>
<td>18–132.3</td>
<td>&lt; 145</td>
<td>16–47</td>
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</tbody>
</table>

DISCUSSION
This is probably the first report on the incidence of Turner syndrome in northeastern Malaysia. The cases presented here are those studied from 2001 to 2006 in the Human Genome Centre of Universiti Sains Malaysia, Kelantan, Malaysia. The first case of probable Turner syndrome was
as reported by Funke, a patient who presented many of the criteria for the syndrome, including lymphoedema, small stature and amenorrhoea at the age of 16 years and pterygium colli. Ullrich collated several cases reported thereafter and identified the first case as the Turner syndrome. In 1938, Turner described a variant of primary amenorrhoea in seven adolescent and young adult females with sexual infantilism, short stature, webbed neck and cubitus valgus. However, it was Sharpey-Shafer who described further cases of this syndrome and coined the term ‘Turner syndrome’. Since then, a number of other karyotype anomalies, such as mosaicsisms and structural anomalies of the second X chromosome, have been found in association with Turner syndrome.

Monosomy X is the most frequent karyotype of the syndrome; next in frequency are the mosaicsisms XO/XX, XO/XXi and XO/XY. Their relative frequencies in the series are 15.5%, 9.3% and 9.0%, respectively. Other karyotype anomalies are rare, and XX Turner syndrome with intrachromosomal changes of the genetic material, such as inversions, is exceptional. In the present study, the incidence of the most frequent karyotype of the Turner syndrome was found to be 45,X (57.1%), followed by 46,X,i(Xq) (21.4%), 45,X/46,X,+mar (7.1%), 45,X/46,X,i(Xq) (7.1%) and 45,X/46,XY (7.1%). In previous studies, the relative frequencies in terms of the most commonly-occurring karyotypes reported in Turner syndrome were 45,X (45%), 45,X/46,XX (13%), 45,X/46,X,i(Xq) (8%), 46,X,i(Xq) (7%) and 45,X/46,XY (7%); although some correlations between karyotype and phenotype have been made, phenotypic predictions for a given patient that are based on karyotypic analysis are unreliable in patients with Turner syndrome.

Two pathogenic mechanisms, which have been described in the literature, lead to monoclonal monosomy
amenorrhoea, the single most common cause is primary
In young women presenting with primary
genes for Turner syndrome.
chromosome have also been identified as the candidate
on the p arm, RPS4X, and DIAPH2 on the q arm of the X
with this condition. In addition, genes USP9X (DFRX)
for the short stature and skeletal abnormalities in women
believe that this deficiency is at least partly responsible
reduces the amount of SHOX protein by half. Researchers
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genes are responsible for the complete phenotype. Short
syndrome indicates that a number of different X-located
was 21 years, with a range from eight to 47 years, and a
 wide range of somatic features have been observed in these
cases. All the patients belonged to the Malay ethnicity and
were from the state of Kelantan. Short stature was the most
common clinical feature present in the cases of Turner
syndromes observed at this centre, followed by primary
amenorrhoea, absence of secondary sexual characteristics, scanty pubic and axillary hair, webbed neck, wide carrying
angle, rudimentary uterus with bilateral streak ovaries, underdeveloped breasts and widely-spaced nipples. In addition to the above characteristics, a history of slow
weight gain, as well as abnormality of the kidney, flat feet, overlying of the fourth toe on the fifth toe bilaterally with osteoporosis of the femoral neck, short metacarpal bones and mental retardation were noticed. Ultrasonographical
findings also indicated hypoplastic left heart in one of our
patients.
The wide range of somatic features in Turner syndrome indicates that a number of different X-located genes are responsible for the complete phenotype. Short
stature in Turner syndrome has been associated with haplo
insufficiency of a critical chromosomal region (distal of
Xp22.2), which escapes inactivation (pseudautosomal region of X and Y) and in which the short stature-
homeobox (SHOX) gene resides (Xp22.33). As a result,
most women with Turner syndrome have only one copy of
the SHOX gene, instead of the usual two copies, which
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believe that this deficiency is at least partly responsible
for the short stature and skeletal abnormalities in women
with this condition. In addition, genes USP9X (DFRX)
on the p arm, RPS4X, and DIAPH2 on the q arm of the X
chromosome have also been identified as the candidate
genes for Turner syndrome.
In young women presenting with primary
amenorrhoea, the single most common cause is primary
ovarian failure due to gonadal dysgenesis. These patients
have significantly elevated gonadotropin levels due to
ovarian failure. Ovarian failure is most commonly
associated with Turner syndrome, followed numerically
by 46,XX gonadal dysgenesis, and rarely, 46,XY gonadal
dysgenesis. Growth retardation is less pronounced and
the clinical picture of the two most frequent mosaicsisms—
XO/XX and XO/XYY—varies between normal female
phenotype and typical Turner syndrome. Moreover, male
phenotypes and intersexes with ambiguous genitalia may
be found in association with XO/XY mosaicism. Women
with Turner syndrome also can have a mosaic pattern
with additional Y chromosome material (45,X/46,XY).
Although this mosaic pattern is uncommon, these
women have an increased risk for the development of
gonadoblastoma, dysgerminoma, and masculinisation, and
prophylactic gonadectomy is warranted.

The mean age of our patients with Turner syndrome
was 21 years, with a range from eight to 47 years, and a
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Although this mosaic pattern is uncommon, these
women have an increased risk for the development of
gonadoblastoma, dysgerminoma, and masculinisation, and
prophylactic gonadectomy is warranted.
The presence of a Y cell line in a patient with Turner syndrome brings
it an increased risk of developing gonadoblastomas and malignant germ cell tumours within the streak
gonads.

Ultrasonographical findings suggestive of Turner syndrome include increased nuchal translucency, cystic
hygroma, coarctation of the aorta or other left-sided cardiac
defects, brachycephaly, renal anomalies, polyhydramnios,
oligohydramnios, and growth retardation. An abnormal maternal serum screen (elevated α-human chorionic gonadotropin) and free β-human chorionic gonadotropin may also suggest Turner syndrome. Ultrasonographical
findings and abnormal maternal serum screen are not sufficient to diagnose Turner syndrome; a karyotype is
required for definitive diagnosis. Chromosomes should always be re-evaluated postnatally because abnormal
prenatal karyotypes may reflect cytogenetic abnormalities found only in the placenta, but not in the foetus.
In addition, inexpensive high-throughput screening is possible for Turner syndrome using quantitative
karyotyping approaches. During the newborn period, physical features characteristic of Turner syndrome include lymphoedema of the hands and feet, nuchal folds, left-sided cardiac anomalies (coarctation or hypoplastic
left heart), webbed neck, and low hairline. During childhood, declining growth velocity with short stature and elevated levels of follicle-stimulating hormone (FSH) should prompt evaluation for Turner syndrome.

There is no causal therapy for Turner syndrome. However, there are several forms of treatment for affected
patients, which include management of cardiovascular, intestinal and renal malformations; treatment of
microsomia; treatment of the gonadal infantilism; cosmetic surgery of the pterygium and counselling of
the parents and of the patients themselves. Psychological
counselling about the patient’s womanhood should be
of utmost importance; they should be advised that they can marry but will need to adopt children if they want to raise a family.\(^8\) The delay in the diagnosis of Turner syndrome in the present scenario could be attributed to the lack of antenatal screening and early neonatal screening. Early diagnosis will enable early intervention and early psychological counselling to the patient as well as the parents, which in turn will help to enhance their quality of life. The institution of societies and referral centres to cater exclusively to the needs of the Turner syndrome patients will also help them to seek advice and improve their outlook towards the society. Hence, establishing early diagnosis, educating and increasing awareness among doctors, as well as prenatal diagnosis, would be an effective measure in alleviating the social trauma related to Turner syndrome patients in this population.

ACKNOWLEDGEMENTS

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