XO/XY mosaicism in phenotypic males

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Abstract

Eight cases of 45 XO/46 XY mosaicism are described: four were phenotypic males. Karyotyping should be performed more frequently in short boys as growth hormone treatment and testicular biopsy, to screen for carcinoma in situ, are likely to be beneficial.

Though the phenotype of 45 XO/46 XY mosaicism is well recognised as variable, ranging from female with gonadal dysgenesis to virtually normal male, most cases in the literature are reported as phenotypic females either as a variant of Turner’s syndrome or with virilisation: only brief mention is made of phenotypic males with this karyotype. A recent report on a series of amniocenteses, however, reviewed 47 cases with XO/XY karyotype and known phenotype, of which 42 (89.4%) were apparently normal phenotypic males. This clearly suggests that the normal male phenotype with XO/XY mosaicism is underdiagnosed, as only short girls and those with ambiguous genitalia routinely have karyotypes in most clinics. We therefore reviewed our experience of children with the 45 XO/46 XY karyotype.

Methods and results

The karyotyping service serves a population of some 320,000 children. Karyotypes are routinely performed on all short girls and those with ambiguous genitalia, including most phenotypic males with hypospadias. There is no way of calculating the completeness of this survey. Since 1981 to the present, 37 phenotypic females with 45 XO or other Turner mosaicism were diagnosed. Eight children were identified with the 45 XO/46 XY karyotype, of whom four presented as short boys, with some stigmata of Turner’s syndrome and hypospadias or cryptorchidism (table). All the boys had phallic lengths within the normal range. Laparotomy was subsequently performed on two, for removal of Mullerian duct remnants in one; unilateral streak ovary and Mullerian tissue were identified in the other. All the palpable testes were scrotal and subject to regular expert examination.

Discussion

In our small series, four cases were detected in phenotypic males with some stigmata of Turner’s syndrome and with minor abnormalities of external genitalia. A notable feature was growth retardation, supporting earlier reports. Given the major bias of ascertainment suggested by Hsu, it seems probable that more short boys have covert XO/XY mosaicism. This raises several issues. It has recently been shown that girls with Turner’s syndrome, including mosaic forms, respond to long term growth hormone treatment with enhanced predicted final height. Assuming the cause of growth failure is similar in these phenotypic males, then they also are likely to respond to growth hormone treatment. We propose a trial of growth hormone in these children. Thus as these children have a potentially treatable form of growth failure, these data suggest that karyotypes

Clinical features and karyotype

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Presuming symptom</th>
<th>Height percentile</th>
<th>Bone age height SD</th>
<th>Bone age velocity SD</th>
<th>Karyotype</th>
<th>Gender of rearing</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>Short stature</td>
<td>&lt;3rd</td>
<td>~2.28</td>
<td>~1.5</td>
<td>XO/XY</td>
<td>Male</td>
<td>Increased carrying angle, shield chest, right and left inguinal hernias, penoscrotal hypospadia, undescended testis (right), left mullerian duct and streak gonad</td>
</tr>
<tr>
<td>2</td>
<td>19</td>
<td>Short stature</td>
<td>&lt;3rd</td>
<td>~1.24</td>
<td>~1.6</td>
<td>XO/XY</td>
<td>Male</td>
<td>Fish mouth, increased carrying angle, shield chest, mid-penile hypospadia, hypoplasia, cryptorchid (left) with rudimentary ovarian tube, uterus, streak gonad, right testis in scrotum</td>
</tr>
<tr>
<td>3</td>
<td>22</td>
<td>Short stature, pubertal delay</td>
<td>&lt;3rd</td>
<td>~3.1</td>
<td>N/A</td>
<td>XO/XY</td>
<td>Male</td>
<td>Shield chest, bilateral undescended testes, penoscrotal hypospadia, bifid scrotum</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>Short stature</td>
<td>&lt;3rd</td>
<td>~2.4</td>
<td>~0.6</td>
<td>XO/XY</td>
<td>Male</td>
<td>Shield chest, bilateral undescended testes, penoscrotal hypospadia, bifid scrotum</td>
</tr>
<tr>
<td>5</td>
<td>0.7</td>
<td>Ambiguous genitalia</td>
<td>25th</td>
<td>~0.2</td>
<td>~0.03</td>
<td>XO/XY</td>
<td>Female</td>
<td>Scrotalised labia, virilised clitoris, single introital opening, shield chest, intra-abdominal testis</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>Short stature</td>
<td>&lt;3rd</td>
<td>~1.43</td>
<td>~1.6</td>
<td>XO/XY</td>
<td>Female</td>
<td>Webbed neck, streak gonads with rudimentary uterus</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>Short stature, 3rd</td>
<td>~1.93</td>
<td>~0.5</td>
<td>1st amenorrhoea</td>
<td>XO/XY</td>
<td>Female</td>
<td>Increased carrying angle, streak gonad</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>Short stature</td>
<td>&lt;3rd</td>
<td>~0.05</td>
<td>~1.9</td>
<td>XO/XY</td>
<td>Female</td>
<td>Webbed neck, shield chest, increased carrying angle, streak gonad</td>
</tr>
</tbody>
</table>

N/A: Not applicable.
should be performed more frequently on short boys. Though it is debatable that all short boys should have a karyotype, certainly those with any stigmata suggestive of Turner’s syndrome, with undescended testes, hypospadias, or with an unacceptable final height warrant one. More aggressive investigation may be necessary as Ayuso et al have reported the case of a pheno-
typic male with 46 XY karyotype from leukocy-
tic cell lines but in whom the 45 XO cell line was observed in skin fibroblasts and gonadal tissue.² One last issue to consider is proper man-
agement of the testes. Obviously if the gonad is intraabdominal, it must be removed as it is likely to be a dysgenetic testis or streak gonad. Dysgenetic testes are presumed to be more prone to neoplastic transformation than streak gonads: Manuel et al calculated a tumour expect-
tancy of over 70% by the third decade.³ It is not
clear, however, that palpable, descended testes really have such a high malignant potential.⁴ ⁵
Testicular biopsy before and after puberty, to
detect carcinoma in situ, may be desirable and
allow either early orchidectomy or bilateral irra-
diation if it is found.⁶

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2 Ayuso MC, Ramos MC, Bello MC, Jiménez A, Cascos AS, 
   Herrera JE. Cytogenetic and clinical findings in ten 45, 
3 Hsu LYF. Prenatal diagnosis of 45X/46XY mosaicism—a 
   of a randomized prospective trial of methionyl human 
   growth hormone and oxandrolone in Turner syndrome. 
5 Manuel M, Katayama K, Jones H. The age of occurrence 
   of gonadal tumors in intersex patients with a 45X/46XY 
6 Muller J. Abnormal infantile germ cells and development of 
   carcinoma in situ in maldescended testes. Int J Androl 
   1987;10:543.

Discovering anaemia at child health clinics

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Abstract
Children at three inner city child health clinics were offered haemoglobin estimation by 
fingerprick blood test when attending for 
immunisation against measles. Of the 98 
immunised, 92 (94%) participated in the 
study, together with 58 other children. 
Anaemia (haemoglobin concentration <110 
g/l) was found in 33 of 130 overall (25%), and 
in 17 of 44 Asian children (39%). The method 
of testing was acceptable to parents and staff.

Iron deficiency anaemia is common among 
toddlers.¹ The reason is usually dietary, and 
contributing factors include late weaning, use of 
ordinary cows’ milk, and weaning on to a diet 
low in iron. It has important effects, including 
recurrent mild infections, poor weight gain, 
behavioural problems, and decreased mental 
performance, all of which may be helped by 
treatment with iron.²

It has been suggested that toddlers should be 
screened for iron deficiency,³ and the recent 
report of the Joint Working Party on Child 
Health Surveillance stated that screening for 
iron deficiency was probably desirable but 
further research is needed.⁴ The first question is 
whether routine blood sampling would be 
acceptable to parents. In this study we have 
looked at this, together with the feasibility of 
setting up a screening programme using 
haemoglobin estimation. We also calculated the 
incidence of anaemia in our community.

Subjects and methods
The study population comprised all children 
attending three inner city child health clinics 
who were due to receive immunisation against 
measles and were aged 15–24 months during the 
six month study period.⁵

Invitation to participate was by letter accom-
panying the reminder about the immunisation 
appointment for children attending two of the 
clinics or by asking the parents when children 
attended for immunisation at the third. Facili-
ties were available to explain the study to 
parents in various Asian languages. Signed 
parental consent was obtained. Children with 
known haematological disorders or diseases 
associated with anaemia were excluded.

We recognised that the study might have a 
detrimental effect on the measles immunisation 
rate. This was monitored during the study and 
and it was decided to stop the study if an appreciable 
decrease occurred.

Capillary blood samples were taken by finger-
prick, collected in 1 ml EDTA bottles and sent 
by routine collection to the hospital laboratory. 
Haemoglobin concentration (normal ≥110 g/l) 
mean corpuscular volume (normal 76–100 fl), 
and mean corpuscular haemoglobin (normal 
27–33 pg) were measured.

A haemoglobin concentration of <110 g/l was 
considered as indicating anaemia, and the 
parents of these children were asked to 
attend the clinic and were given dietary advice (with 
the aid of the community dietician). Those 
who had haemoglobin concentrations of <95 g/l 
were given oral iron supplements and further 
investigations including electrophoresis and 
estimation of serum ferritin concentration 
undertaken. All anaemic children were followed 
up to ensure that they responded to diet or iron. 
If another cause of anaemia or lack of response 
was found, appropriate follow up was arranged.

The study was undertaken with the usual