Bone maturation in girls with Turner’s syndrome

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Abstract

The mechanism of growth retardation in Turner’s syndrome has not been resolved. It is often referred to as a bone dysplasia, although endocrine derangement has not been ruled out. The present study was undertaken to evaluate the maturation of individual bones of the hand and wrist in girls with Turner’s syndrome and thereby obtain information which may aid in elaborating the possible mechanism of the growth retardation in girls with Turner’s syndrome. Hand and wrist films of 24 girls with Turner’s syndrome, 11 normal girls with short stature and 23 normal controls were evaluated, using the references of Greulich and Pyle. Each bone or epiphysis was given an individual ‘age’. During childhood the Turner patients showed the greatest delay in bone age of the phalangeal bones while the least delayed were the radius and ulna (long bones) and metacarpals. The carpal bones showed intermediate retardation. This pattern and extent of maturational retardation was clearly different from that of the short stature normal group, who showed uniform retardation of all bones. During adolescence, the phalangeal bones were further retarded and the carpal bones showed a moderate retardation. The unique profile of bone maturation in Turner’s syndrome suggests an insult to chondroplasia, which may be related to estrogen deficiency or to an as yet undetermined endocrine or paracrine derangement.

Introduction

The mechanism of growth retardation in Turner’s syndrome has not been resolved. The combination of short stature with irregular metaphyses, vertebral anomalies and Madelung’s deformity (1, 2), lead to the assumption that Turner’s syndrome is a bone dysplasia, although the radiological findings do not conform with the definition of any of the known bone- or chondrodysplasias. The most common bones which clinicians usually look at in such patients are the hand and wrist bones, radiographed for the purpose of assessing a ‘bone age’. This rough measure of bone maturation gives limited information of growth potential in girls with Turner’s syndrome, and clinicians resort to a projection of adult height by an extrapolation from disease-specific growth curves.

Initial analyses of hand and wrist bones were reported over two decades ago (3, 4). Metacarpal and phalangeal bones were reported to be shorter and narrower in Turner patients, with increasing growth deficiency from distal to proximal and from lateral to medial bones. In adult Turner patients the surface areas of carpal bones were reported to be smaller (5) or not different (6) from adult controls, and increased with estrogen replacement. A later report confirmed a delay in bone maturation in both prepubertal and pubertal Turner girls (7).

X-ray films of the hand and wrist, however, contain potentially more informative findings on the mechanism of growth retardation. The differential maturation pattern of the cuboid bones of the wrist from that of the short bones of the hand or the long bones of the arm, may signify differential hormonal or growth factors effects on these various bones.

In the present report we describe the evaluation of maturation of individual bones of the hand and wrist in girls with Turner’s syndrome and compare them to those of a control group of normal sized girls and a control group of girls with short stature. We show the age-related changes in these bones and attempt to use the results to suggest possible mechanisms which may be affected in the bone maturation of girls with Turner’s syndrome.

Patients and methods

The age and height characteristics of the subjects used in this study are presented in Table 1. In all 24 patients with Turner’s syndrome the diagnosis was confirmed by chromosomal karyotyping, and included patients with 45,X, 45X,iXq or mosaics. The girls were divided into a preadolescent group (aged 4.6–10 years, n = 13) and an adolescent group (aged 10.1–14.7 years, n = 11). For each patient a single retrospective radiograph was
reviewed, and that image was chosen to give a wide range of ages and to include no patient with spontaneous puberty or on any hormonal replacement. The control group and the short normal group were age-matched to the Turner patients and retrospectively selected from the patients of our clinic. Girls in the short normal group (n = 11) were those referred to us with height that was smaller than −2 S.D.s and who had a growth velocity of more than −1 S.D.s, regardless of their parents’ height. Retrospectively, in view of their delayed bone maturation, most of these girls had constitutional delay of growth and puberty. Normal control girls (n = 23) were age-matched and of normal height and growth velocity.

Bone maturation was assessed by a single observer through evaluation of each individual bone, as shown in Fig. 1, by the standards of Greulich and Pyle (8). Each film was evaluated on three separate occasions and the results did not deviate by more than three months in any of the films. Whereas the TW-2 method (9) requires the joint scoring of either the entire plate or the radius, ulna and short bones (RUS), the Greulich and Pyle method allows for evaluation of each individual bone in terms of ‘years’. For statistical comparison of girls of different ages, the reading for each bone is given in terms of ‘years’ of delay against the chronological age, and the standard deviations of values of the two control groups were evaluated against the results of each group by a Student’s t-test.

**Results**

Table 2 presents the individual bone maturation in units of ‘years’ of retardation relative to the respective chronological age. It is divided into girls up to 10 years of age, and girls older than 10 years. This cut-off age was elected as the mean age of the onset of puberty in normal girls when, under estrogenic activity, bone maturation accelerates and on a theoretical basis the gap between Turner’s syndrome and normal control groups would increase.

The control normal girls showed a slight advancement of bone maturation of 0.3–0.9 ‘years’ that was not significantly different from the standards. In the younger age group Turner patients the phalangeal bones were the most retarded with a mean retardation of 1.7–1.8 ‘years’; the least retarded were the ‘long bones’ and the metacarpals, with a mean retardation of 0.8–1.1 ‘years’. The carpal bones showed intermediate retardation of 1.4–1.5 ‘years’. This pattern and extent of maturational retardation was clearly different from that of the short normal group. In that group all of the bones were retarded to a similar extent, with an average 1.8–2.7 ‘years’ of retardation.

The older group (>10 years) of normal controls was similar to the standards. In the older age group, Turner patients showed a further delay of maturation in the entire image. The phalangeal bones were further retarded, with a mean retardation of 2.7–3.1 ‘years’. The ‘long bones’, the metacarpals and the carpal bones showed a moderate retardation of an average 1.5–2.1 ‘years’. This pattern and extent of maturational retardation was clearly different from that of the short normal group in whom all of the bones were retarded to a similar extent with an average narrow range of 2.2–2.6 ‘years’ of delay.

A third degree regression of specific bones against age emphasize the unique pattern of bone retardation in Turner’s syndrome (Fig. 2). Whereas in the two control

**Table 1 Age and height characteristics of girls in the Turner syndrome group (n = 24), the short normal group (n = 11) and the control group (n = 23). Results are means ± S.D.**

<table>
<thead>
<tr>
<th></th>
<th>Turner’s syndrome</th>
<th>Short normal</th>
<th>Normal control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>10.8 ± 0.9</td>
<td>9.7 ± 1.0</td>
<td>10.0 ± 0.9</td>
</tr>
<tr>
<td>Height (S.D.s)</td>
<td>−3.0 ± 1.2</td>
<td>−2.3 ± 1.1</td>
<td>0.3 ± 1.1</td>
</tr>
</tbody>
</table>

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**Figure 1** Diagramatic presentation of hand and wrist bones. Bone numbers are explained in Table 2.
Table 2 Individual bone maturation assessed by the Greulich and Pyle method. Results are given in ‘years’ of delay behind the chronological age for thirteen preadolescent Turner syndrome (TS) girls (aged 4.6–10 years) and for eleven adolescent TS girls (aged 10.1–14.7 years). Age-matched normal short (SS) and control groups are also included. Bone numbers (in parentheses) are those shown in Fig. 1. Results are means ± s.d.

<table>
<thead>
<tr>
<th>Bone</th>
<th>Preadolescent</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TS</td>
<td>SS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radius (1)</td>
<td>−1.1 ± 1.6</td>
<td>−2.0 ± 1.4</td>
</tr>
<tr>
<td>Ulna (2)</td>
<td>−0.8 ± 1.1</td>
<td>−1.3 ± 1.0</td>
</tr>
<tr>
<td>Prox. Ph. (3–7)</td>
<td>−1.8 ± 1.4</td>
<td>−2.2 ± 1.0</td>
</tr>
<tr>
<td>Mid. Ph. (8–11)</td>
<td>−1.8 ± 0.9b</td>
<td>−2.5 ± 1.3b</td>
</tr>
<tr>
<td>Dist. Ph. (12–16)</td>
<td>−1.7 ± 1.2</td>
<td>−2.4 ± 1.1b</td>
</tr>
<tr>
<td>Metacarpals (17–21)</td>
<td>−1.1 ± 1.6</td>
<td>−2.6 ± 1.6b</td>
</tr>
<tr>
<td>Capit. &amp; Hamate (22–23)</td>
<td>−1.5 ± 1.6</td>
<td>−2.5 ± 1.4</td>
</tr>
<tr>
<td>Pisif. &amp; Triq. (24–25)</td>
<td>−1.4 ± 1.6</td>
<td>−1.8 ± 1.4</td>
</tr>
<tr>
<td>Lunate (26)</td>
<td>−1.5 ± 1.7</td>
<td>−3.4 ± 2.1c</td>
</tr>
<tr>
<td>Scaphoid (27)</td>
<td>−1.8 ± 1.2</td>
<td>−2.4 ± 1.7a</td>
</tr>
<tr>
<td>Trapezoid (28)</td>
<td>−1.3 ± 1.3</td>
<td>−2.2 ± 1.5a</td>
</tr>
<tr>
<td>Trapezium (29)</td>
<td>−1.1 ± 1.4</td>
<td>−3.0 ± 1.8b</td>
</tr>
</tbody>
</table>

* P < 0.05, ** P < 0.01, *** P < 0.005 compared with control group.
Prox. Ph., proximal phalanx; Mid. Ph., middle phalanx; Dist. Ph., distal phalanx; Capit., capitale; Pisif., pisiform; Triq., triquetsal.

Figure 2 Third degree regression of the delay (d) in bone maturation against chronological age in the short normal group (SS), the control group (Ctr) and the Turner’s syndrome group (TS).

groups. ‘long bones’, ‘short bones’ and carpals show parallel regression with narrow gaps, the pattern in the Turner patients showed a milder delay in the ‘short bones’ during early puberty, with increased delay during adolescent age. The carpals and ‘long bones’ were relatively more retarded in prepuberty, and less so in adolescence.

**Discussion**

As the TW-2 method for evaluation of bone maturation was developed, Tanner et al. realized that the ‘long bone’ and ‘short bone’ readings (RUS) show a discrepancy with the carpals in many clinical conditions (9). They proposed, however, that the mean difference between carpals and RUS in normal girls is 0 ‘years’ during 2–11 years of age, with an S.D. of 0.7–1.0 ‘years’. In the present study we took a similar approach, expanded it to readings of individual bones and attempted to obtain an insight from these readings into the mechanisms of growth retardation in Turner’s syndrome. In order to deal with bone ‘age’ of individual bones, and to give the readings in terms of ‘years’ of delay for each individual bone we had to use the Greulich and Pyle method (8).

The overall tendency of bone maturation in Turner’s syndrome is for prepubertal milder retardation of all the bones compared with short normal girls. Retardation of the short bones, and to a milder extent that of the long bones and carpals, increase after the age of ten. This pattern is consistent with growth curves of Turner patients (10, 11), where growth retardation during early childhood is relatively mild, increasing towards late childhood to become severe during adolescence.

Of the many still obscure aspects of the growth retardation in Turner’s syndrome, one obvious factor is
estrogen deficiency. This deficiency becomes dominant during adolescence; however it has recently been appreciated that estrogen deficiency may also have some impact during childhood (12). It is assumed, therefore, that the unique pattern of bone maturation during adolescence in these untreated girls with Turner’s syndrome is a pattern of estrogen deficiency, which is characterized by severe retardation of phalangeal epiphyses, and milder retardation of radius, ulna, metacarpals and carpals. But this hypothesis needs to be addressed in a study of bone maturation in girls with estrogen deficiency from other causes. If this is to become the maturational profile of estrogen deficiency, it is obvious that some estrogen deficiency prevails in Turner’s childhood, as here too the phalangeal epiphyses are the most retarded.

It is, however, possible that this profile has to do with another, unknown endocrine derangement of Turner’s syndrome, leading to the characteristic growth retardation and its specific ‘bone dysplasia’. By convention, the appearance on an X-ray film of secondary ossification centers in the epiphyses of ‘long bones’ and of ‘short bones’ during early childhood is referred to as the process of ‘osteogenesis’. It is followed by development and expansion of the growth plate cleft, a process referred to as ‘chondroplasia’ (13). Primary ossification of the cuboid carpals bones develops through ‘osteogenesis’. The profile of bone maturation in Turner’s syndrome suggests a major insult to chondroplasia. During the younger age group, when both cuboid and long bones reflect osteogenesis, the entire profile of Turner patients was less delayed, as compared with the short normal group. Later on, as long bone epiphyses develop to represent chondroplasia, the maturational profile portrays a greater retardation of the phalangeal epiphyses. In descriptive terms, the insult to chondroplasia can be defined as ‘epiphyseal dysplasia’.

To combine these two approaches, it can be envisioned that estrogen deficiency results in an insult to chondroplasia. Yet, chondroplasia is not influenced only by estrogen. A large volume of literature has been devoted to the regulation of enchondral ossification by growth hormone (GH), insulin-like growth factor (IGF)-I and local growth factors (13). In that respect, serum GH has been reported to decrease during the adolescence of girls with Turner’s syndrome (14) and recent indirect evidence has suggested that the growth retardation in Turner’s syndrome may be linked to decreased sensitivity to IGF-I (15).

The enigma of growth retardation in Turner’s syndrome has yet to be solved. Future research may be directed to the potential insults to chondroplasia by estrogen deficiency. IGF-I decreased sensitivity, or otherwise.

Acknowledgements
We thank Drs I Sills and H Gutman for letting us review their patients’ X-rays and Professor M Jaffe for critical reading of the manuscript.

References

Received 25 April 1997
Accepted 29 September 1997