Palatal height and dental arch dimensions in Turner syndrome karyotypes

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SUMMARY The aim of this project was to study the impact from Turner syndrome (TS) karyotype and age on dental arch morphology and palatal height and to compare the variables in TS with reference data from non-TS females with normal occlusion. Plaster casts from 76 females with TS (6–50 years) were analysed with respect to dentoalveolar arch dimensions and palatal height. The TS females were divided into the karyotype categories: i) 45,X ii) 45,X/46,XX iii) isochromosome, and iv) other.

The 45,X/46,XX karyotype exhibited fewer statistically significant variables differing from the reference group compared with other karyotypes. TS females showed increased dentoalveolar depths, decreased maxillary but increased mandibular width, decreased posterior segments, and decreased mandibular circumference compared with the reference group. In opposition to previous reports, the palatal height did not differ compared with non-TS females. Age had an impact on nine of the variables. We conclude that the present dental arch deviations are reflecting the high frequency of malocclusions reported in TS and the subsequent need for orthodontic treatment, which might possibly be lower in the 45,X/46,XX karyotype. The palatal height did not differ from the reference group, but instead the narrow maxilla might contribute to an illusion of a higher palate. We therefore suggest using the nomination ‘narrow palatal vault’ instead of the commonly used term ‘high palatal vault’.

Introduction

Turner syndrome (TS) occurs in females as a result of the absence or aberration of one of the X chromosomes in all or a proportion of cells (Nielsen and Wohler, 1990; Gravholt et al., 1996). The principal clinical effects of the chromosomal alteration are related to growth retardation, and short stature is the main feature of TS (Lippe, 1991; Saenger et al., 2001). The growth impairment in TS also affects the craniofacial skeleton, giving a flattened cranial base in addition to retrognathic maxilla and mandible (Jensen, 1985; Peltonäkki et al., 1989; Rongen-Westlaken et al., 1992; Babic et al., 1993; Midtbø et al., 1996; Simmons, 1999; Hass et al., 2001; Perkiömäki et al., 2005; Rizell et al., 2012b). Additionally, when compared to healthy female controls, the prevalence of malocclusions is increased (Laine et al., 1986; Midtbø and Halse, 1996; Szilágyi et al., 2000), and the dental arch dimensions are reported to deviate (Filipsson et al., 1965; Laine et al., 1985; Ogiuchi et al., 1985; Laine and Alvesalo, 1986; Szilágyi et al., 2000). A high arched palate is regarded as a significant clinical feature for TS that, if combined with one additional stigmata, is indicative for karyotype analysis, a prerequisite for the TS diagnosis (Lemli and Smith, 1963; Ogiuchi et al., 1985; Zinn et al., 1998; Szilágyi et al., 2000; Sävendahl and Davenport, 2000; Ross et al., 2001; López et al., 2002; Rappold et al., 2007). In TS, geno-phenotype correlation studies on palatal height are rare, but show that a high arched or dysmorphic palate is more common in 45,X than 45,X/46,XX karyotype (El-Mansoury et al., 2007, Makishima et al., 2009). A shortcoming with these studies is that their findings are based on visual assessment of the palatal height only. To our knowledge and to this date, no studies of karyotype correlations on palatal height measured on cast models are published.

An increased number of sex chromosomes is another interesting matter, as an influence on palate and dental arch size has been reported in both 47,XXY (Klinefelter syndrome) and 47,XY (Laine and Alvesalo, 1993a, 1993b). A high arched palate together with other skeletal deformities are proposed to be caused by a deletion or mutation of the SHOX gene, which is located on the short arm (p-arm) of the X or Y chromosome (Clement-Jones et al., 2000; Ross et al., 2001; El-Mansoury et al., 2007; Rappold et al., 2007). Since haploinsufficiency of the SHOX
gene seems to affect the skeletal growth in several parts of the body, it is feasible to assume that SHOX has an impact on dental arch morphology and palatal height that differs according to TS karyotype. To date no such study on geno-phenotype correlations on neither dental arch dimensions nor palatal height is available.

The aim of this project was to study the impact from TS karyotype and age on dental arch dimensions as well as palatal height and compare these variables in TS with normative data from non-TS females with normal occlusion.

Subjects
In the regions of Gothenburg, Uppsala and Umeå in Sweden, 132 females with TS gave their written consent to take part in this project. Seventeen females were excluded since their dental records were of poor quality or missing. Thirty-one individuals were excluded since they had a history of orthodontic treatment. Another seven individuals were excluded because they had extensive dental restorations or tooth loss and one girl since she was born with a total unilateral cleft, giving a total number of 76 cases with a mean of 15.2 years of age, ranging from 6 to 50 years. In the present group of TS females, 75% had been treated with growth hormone. Genetic karyotyping was undertaken by routine chromosomal analysis of peripheral lymphocytes. The TS females were grouped into four karyotype categories: i) 45,X; ii) 45,X/46,XX; iii) isochromosome, and iv) other (Table 1).

The TS isochromosome karyotype has one normal X chromosome and one isochromosome displaying two identical arms (duplication of the long q-arm) and consequently a loss of one short p-arm.

Methods
Plaster casts were made from impressions of the upper and lower dentition. The measurements of dental arch width, depth, length of anterior and posterior segments, total circumference, and palatal height were performed according to Thilander (2009) using a modified digital calliper (Figures 1a and 1b). The dentoalveolar depth was measured at the level of the second premolar, the intermolar width at the level of the first molar, and the interpmolar width at the level of the second premolar. In cases with frontal spacing the distal landmark for the anterior segment and the mesial landmark for the posterior segment was set in the midpoint of the approximal space between the canine and the lateral and the mesial landmark for the anterior segment in the midpoint of the median diastema. All measurements were made by one investigator (SR), who was blinded for the karyotype of the females during the measurements. The measurements of dental arch and palatal height were converted into age and gender-specific standard deviation scores (SDS) using published normative data from a group of Swedish females with normal occlusion and no history of orthodontic treatment (Thilander, 2009). The reference values were used as a ‘golden standard’ and counted as zero.

Table 1 The distribution of Turner syndrome (TS) karyotypes.

<table>
<thead>
<tr>
<th>Karyotype category</th>
<th>TS karyotype</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>45,X</td>
<td>29 (38)</td>
</tr>
<tr>
<td>2</td>
<td>45,X/46,XX</td>
<td>9 (12)</td>
</tr>
<tr>
<td>3</td>
<td>Isochromosomes</td>
<td>19 (25)</td>
</tr>
<tr>
<td>4</td>
<td>X chromosome deletion</td>
<td>3 (25)</td>
</tr>
<tr>
<td></td>
<td>X chromosome translocation</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>X chromosome inversion</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Marker chromosomes</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Ring chromosomes</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Y chromosomal material</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>45,X/47,XXX</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>76 (100)</td>
</tr>
<tr>
<td>Mean age, years</td>
<td></td>
<td>15.2</td>
</tr>
<tr>
<td>Age range, years</td>
<td></td>
<td>6.0–50.0</td>
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</tbody>
</table>
To calculate SDS the difference between the actual value and the mean of the specific age group of the population was divided by the standard deviation for the population. A SDS value close to zero reflects similarity with the reference group, while a positive SDS means a higher value and subsequently a negative SDS means a lower value than the reference group. For calculation of the intra-individual error of measurement, the dental arch and palatal height measurements were performed twice with more than one month interval on sixteen randomly chosen plaster casts (Dahlberg, 1940). The error of measurement ranged from 0.18 to 0.59 mm. The study was approved by the University of Gothenburg ethics committee.

Statistics

One sample t-test was used to analyse the dental arch and palatal height differences against the normative data from the reference group of non-TS females (Thilander, 2009) for the entire TS group as well as for each karyotype group separately. Analysis of covariance (ANCOVA) was used to study impact from karyotype and age on dental arch and palatal height variables. P-values less than 0.05 were considered as statistically significant.

Results

Compared with the reference group, the TS females had a larger maxillary and mandibular dentoalveolar depth (P < 0.001), smaller maxillary interpremolar and molar width (P < 0.001 and P < 0.01, respectively), larger mandibular interpremolar and molar width (P < 0.001), shorter posterior segments in both maxilla (P < 0.05) and mandible (P < 0.01), and also a shorter mandibular circumference (P < 0.01) (Table 2). On comparison of each karyotype separately with non-TS females, the 45,X/46,XX group showed fewer dentoalveolar arch and palatal height variables differing from the reference group compared with the other karyotype groups (Table 2). Analysis of covariance could not prove impact from karyotype on the measured variables, while age had an impact on nine of the variables (Table 3). From these nine variables, only the mandibular intermolar width was deviating more from the reference group in an age-dependent manner, i.e. with increasing age the mandible in TS was broader relatively to the reference group (Table 3, Figure 2).

Table 2 Results, displayed as mean standard deviation scores (SDS) and P-values, from comparison of mean SDS for the palatal height and dental arch variables from all Turner syndrome (TS) individuals as well as for each karyotype group, one by one against the female reference data (Thilander, 2009) using one sample t-test.

Table 3 Variables showing a statistically significant impact from age or karyotype on dental arch variables, converted into age specific SDS using a female reference (Thilander, 2009). The impact from the remaining variables, not displayed in Table 3, was not statistically significant. A positive regression coefficient indicates a positive correlation, while a negative regression coefficient indicates a negative correlation.
Discussion

The new finding in this study was that the dental arch dimensions in 45,X/46,XX karyotype were close to normal and that compared with the 45,X and isochromosome groups, 45,X/46,XX karyotype seemed to have less variables differing from non-TS females. To our knowledge and to date, no previous cast model studies are found on karyotype correlations on dental arch dimensions or palatal height. When comparing TS with normative data from non-TS females for the transversal variables, our results showing a decreased maxillary width but increased mandibular width are in accordance with previous publications (Filipsson et al., 1965; Laine et al., 1985; Ogiuchi et al., 1985; Laine and Alvesalo, 1986; Szilágyi et al., 2000). For the sagittal measures, however, results are contradictory, as the present finding of an increased maxillary arch depth (also named ‘arch length’) is in line with Laine et al., (1985) but disagree with studies by Szilágyi et al. (2000) and Ogiuchi et al. (1985). Our finding of an increased mandibular arch depth is contradictory to previously mentioned reports, which possibly is due to methodological differences. In the mentioned studies, both the growing and the adult individuals were included, but no age matching against the controls was performed, and a different distribution of TS karyotypes than ours constitutes other methodological disparities compared with the previous studies. Additionally, none of the other publications used females with a normal occlusion as reference group, but their relatives, short stature girls or different samples of healthy females. Often only 45,X cases were included in the analyses. In the present study, conversion of the dental arch variables into age specific SDS, together with our multicentre study design, which enabled separation into fairly large karyotype groups, is regarded a strength.

The present results confirm earlier findings about a narrow maxilla and a broad mandible in TS (Filipsson et al., 1965; Laine et al., 1985; Ogiuchi et al., 1985; Laine and Alvesalo, 1986; Szilágyi et al., 2000). Perkiömäki and Alvesalo (2008) observed an increased distance between the tongue and the palatal plane in TS, indicating a low position of the tongue. Such a position of the tongue is claimed to cause an imbalance between the pressure from the cheek and the tongue and increases the relative pressure from the cheeks on the maxillary arch, which, therefore, is narrowing (Perkiömäki and Alvesalo, 2008; Takada et al., 2011; Primozic et al., 2012). Consequently, the mandibular arch is widening because of the increased pressure from the tongue. The narrow maxilla, the broad mandible and the increased maxillary arch depth found in the present study also reflects previous reports on an increased occurrence of distal molar relation, large overjet and lateral crossbite (Laine et al., 1986; Harju et al., 1989; Midtbø and Halse, 1996; Szilágyi et al., 2000). Our finding of an increased dentoalveolar depth compared with the reference group also in the mandible is not necessarily mutually exclusive to the reports of large overjet, since the maxillary dentoalveolar depth SDS was +1 SDS higher compared with the mandibular dentoalveolar depth SDS. We found that the posterior segments were
shorter both in the maxilla and the mandible as well as the mandibular circumference, which might reflect a mesial migration of posterior teeth due to a decreased tooth width (Rizell et al., 2012a). No previous studies about the length of the dental arch segments in TS are found.

The reported prevalence of a high arched palate in TS varies from 18 to 100 % (Lemli and Smith, 1963; Gorlin et al., 1965: Johnson and Baghdady, 1969; Laine et al., 1985; Ogushi et al., 1985; Zinn et al., 1998; Szilágyi et al., 2000; Sävendahl and Davenport, 2000; Ross et al., 2001; López et al., 2002; El-Mansoury et al., 2007; Rappold et al., 2007; Perkiömäki and Alvesalo, 2008; Makishima et al., 2009). However, the majority of these studies are based on visual judgements only. Three out of the five studies that measured the palatal height on cast models were performed on limited samples (≤18 cases) (Gorlin et al., 1965; Johnson and Baghdady, 1969; Horowitz and Morishima, 1974). Only Laine et al., (1985) had a sufficient number of participants for statistical analysis and found that the height of the palatal vault in TS, with exception from the canine area, equalled the height in controls. Our results with no difference between TS and non-TS females at the molar level support that finding. There are reports of presence of lateral palatal ridges, which together with the narrower maxillary arch might give the palatual vault a false appearance of being higher (Laine et al., 1985; Perkiömäki and Alvesalo, 2008). The position of the tongue is thought to be of importance for development of the lateral palate ridges, which constitutes bulges of fibrous tissue appearing between the palatal midline and the alveolar processes (Perkiömäki and Alvesalo, 2008). It is found that during normal development these ridges are present during foetal life and they are gradually smoothed out postnatally by the moulding force from the tongue, which in TS is found to have a lowered position (Hanson et al., 1976; Perkiömäki and Alvesalo, 2008).

Age had an impact on several of the dental arch measures. It was most evident for the mandibular intermolar width, which was the only variable aggravating compared with non-TS females, with increasing age, in this case a relatively wider intermolar width (Figure 2). This seems to be in contrast to our previous findings that older TS females had a more deviant mandibular morphology and retrognathism than younger females (Rizell et al., 2012b). However, conclusions are difficult to draw since the individuals in the older age spans were few.

A substantial portion of the participants was excluded due to previous orthodontic treatment. When such a major portion of the participants has had orthodontic intervention, there is a risk of losing information when they are excluded from the investigation, since the group that needed orthodontic treatment might have been the most deviant. On the other hand, including them would possibly have biased the results. We choose to exclude the previously treated individuals, since we anticipated that an eventual subtle influence from karyotype might be obscured from the effects from orthodontic treatment. No statistically significant differences between the groups with or without orthodontic treatment regarding karyotype distribution could be proven. This may indicate that there was not an over-representation of a certain karyotype in the treated group.

The choice of normative data from females with normal occlusion might be questioned (Thilander, 2009). The optimal the reference group might have been a group of mothers and sisters to escape bias from an underlying hereditary pattern. However, the choice of the Swedish reference material made it possible to escape bias from eventual racial differences, which was a predominant advantage with the choice of this reference group. It is of course important to be aware that only using females with normal occlusion as reference group might have given more deviating results than using a female population group with different kinds of malocclusions.

Interestingly, growth of the dental arches may also be influenced by the number of sex chromosomes (Laine and Alvesalo, 1993a, 1993b). Grön and Alvesalo (1997) concluded that the Y chromosome, in 46,XY women with complete testicular feminization, created dental arches with measures falling between those of normal females and males. It is suggested that several TS features map to the short arm of the X chromosome (Ogata and Matsuo, 1995). By studying deletions located in different parts on the p-arm, a locus for high arched palate or other TS traits has been mapped to the Xp11.2-p22.1 region (Zinn et al., 1998). The SHOX gene is located at Xp22.33 in the pseudoautosomal region (PAR), where the haploinsufficiency of the gene, by definition, is affecting the dosage of the protein and thereby causing impaired growth (Burgoyne, 1982; Ross et al., 2001). SHOX is expressed in two major regions, the limbs and the first and second pharyngeal arches, and is believed to be involved in the growth impairment causing short stature in children with TS (Clement-Jones et al., 2000; Rappold et al., 2007). However, children with SHOX gene anomalies have also been described as having a high percentage of high arched palate, and it is therefore feasible to assume that a haploinsufficiency is an underlying factor for the abnormal growth, causing the deviations found on the dental arch dimensions (Salmon-Musial et al., 2001). The 45,X/46,XX karyotype has previously been described as exhibiting a milder phenotype with fewer aberrations from controls compared with other karyotypes, concerning spontaneous pregnancies, fine motor function, body balance, hearing, presence of TS stigmata, tooth width and craniofacial morphology (El-Mansoury et al., 2007; El-Mansoury et al., 2009; Bryman et al., 2011; Rizell et al., 2012a,b). The presence of healthy cell lines among these females might be one explanation for the milder phenotype we found for the dental arch variables.

It has previously been discussed about the hypothesis of the retarded fibroblast cell division rate, which causes a prolonged cell cycle in 45,X (Simpson and Lebeau, 1981;
Verp et al., 1988). Also an increase of the cellular genetic material i.e. trisomy of cells can slow down the cell division (Paton et al., 1974; Simpson and Lebeau, 1981). To our knowledge, no articles on cell cycle time in TS isochromosomes are published. There are suggestions that a longer cell generation time during critical developmental periods can cause an irreversible growth disturbance, either due to reduction of cell number or due to delayed timing from signalling of growth factors, in susceptible areas, with short developmental time windows (Diewert, 1985; Barrenäs et al., 2000). Our results with 45,X being one of the karyotypes with more variables differing from the reference group support that theory.

Conclusion

We found that the 45,X/46,XX karyotype mitigated the aberrances generally seen among TS females regarding dental arch dimensions as they exhibited fewer variables differing significantly from the reference group than other karyotypes. Additionally, TS females seem to have a longer and narrower maxillary arch as well as a longer but wider mandibular dental arch. Age had an impact on nine of the dental arch variables. The dentoalveolar arch changes found in this study reflect the high frequency of malocclusions reported in TS as well as the subsequent need for orthodontic treatment. This study could not prove any difference in palatal height comparing TS to the reference group. It is possible that the narrower dental maxillary arch in combination with presence of lateral palatal ridges, gives the false illusion of an increased palatal height, a clinical finding often described for genetic disorders. We, therefore, suggest the denomination 'narrow palatal vault' instead of using the term 'high palatal vault' for the typical TS feature.

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