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Research paper

Ear and hearing problems in relation to karyotype in children with Turner syndrome

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ABSTRACT

The aim of the study was to report otologic and audiologic characteristics in a group of children with Turner syndrome (TS) and correlate these findings to karyotype. Additionally, we give recommendations for the otologic care of these children. Sixty children (age 1.7–21.2 years) were included in this retrospective study. Medical history and karyotypes were recorded and otologic and audiologic evaluation was performed. A history of recurrent otitis media was reported in 41/60 (68%) children and 3/60 (5%) had suffered from cholesteatoma. Audiometric data in 56 children revealed that normal hearing was only present in 33/112 (29%) ears. All other ears 79/112 (71%) were classified in five different audiometric categories for hearing loss. Hearing thresholds in general appeared to be about 10–11 dB worse in children with a monosomy 45,X or isochromosome (both have a total deletion of the short (p) arm of the X-chromosome) compared to those having a mosaicism or structural anomaly (partial deletion, or total deletion in only a few cells). Our findings support the hypothesis that hearing can be affected by loss of the p-arm of the X-chromosome. It is for the first time that a relation between hearing problems and karyotype is statistically confirmed in a large group of children with TS.

1. Introduction

Turner syndrome (TS) is a relatively common chromosomal disorder, occurring in approximately 1 in 2.000 live-born females (Ranke and Saenger, 2001). TS is caused by a total or partial deletion of one X-chromosome. Monosomy 45,X, having only one X-chromosome in all cells, is the most frequently occurring karyotype (50%). Thirty to forty percent of the patients have a mosaicism, with two or more chromosomally different cell lines, for example 45,X/46,XX; 45,X/47,XXX or 45,X/46,XY. Other patients have structural sex chromosome anomalies such as deletions or ring chromosomes. There are also karyotypes with a duplication of the long arm of the X-chromosome (isochromosome, 46,X,i(Xq)) (Gravholt, 2004; Ranke and Saenger, 2001; Sybert and McCauley, 2004).

The main characteristics of TS are short stature and ovarian dysgenesis. Girls with TS are usually treated with growth hormone to increase adult height by several inches and with estrogen to induce puberty (Gravholt, 2004; Ranke and Saenger, 2001). Other possible clinical manifestations are a webbed neck, lymphedema, a broad chest with widely spaced nipples, a low posterior hairline and cubitus valgus. TS patients are at risk for cardiovascular disease, renal malformations, hypothyroidism, diabetes mellitus, dyslipidemia, hypertension, and osteoporosis (Gravholt, 2004; Hall and Gilchrist, 1990; Ranke and Saenger, 2001; Sybert and McCauley, 2004).

Auricular malformations, middle ear disease and hearing impairment are commonly seen in TS. The external ear anomalies have been described as low set ears, cupped auricles, narrowing of the external auditory canal and abnormally protruding ears (Barrenas et al., 1999; Dhooge et al., 2005; Stenberg et al., 1998).

Chronic or recurrent otitis media is frequently seen in young and adolescent females with TS, resulting in conductive hearing loss (CHL) (Anderson et al., 1969; Serra et al., 2003; Stenberg et al., 1998). Many TS patients have an abnormal craniofacial morphology. A retarded development of the cranial skeleton, an unusual downward

Abbreviations: TS, Turner syndrome; CHL, conductive hearing loss; SNHL, sensorineural hearing loss; MHL, mixed hearing loss; dB HL, dB hearing level; AC, air conduction; BC, bone conduction; ABG, air-bone gap; p-arm of X-chromosome, short arm of X-chromosome.

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slope of the external auditory canal and palatal anomalies such as a high arched palate are frequently seen (Anderson et al., 1969; Filipsson et al., 1965; Gungor et al., 2000; Makishima et al., 2009; Midtbo et al., 1996; Sculerati et al., 1990). These findings have impact on the Eustachian tube function causing recurrent middle ear infections. A subnormal immune response and the effect of X-chromosome related hormonal impact have also been put forward as contributing factors (Anderson et al., 1969; Stenberg et al., 1998).

Women with TS often develop a mid-frequency sensorineural hearing loss (SNHL) (basin-shaped, maximum around 1–2 kHz) in their teens or adolescence. As long as the higher frequencies are still well heard, this usually does not cause hearing problems. The mid-frequency loss usually occurs in women with the karyotype 45,X and 46,X,i(Xq). In these karyotypes, the short (p) arm of the X-chromosome is missing, which suggests that the locus for hearing impairment in TS may be located on this arm (Hultcrantz et al., 1994; Hultcrantz, 2003; Hultcrantz and Sylven, 1997). Furthermore, a progressive high-frequency SNHL is associated with TS (Hultcrantz, 2003).

The rate of hearing decline is much higher in women with TS than in age-matched women in the general population. It is suggested that the karyotypes 45,X and 46,X,i(Xq) but, even more, the presence of a mid-frequency loss, is a high predictive value for rapid decline in the high-frequencies (Hederstierna et al., 2009). CT-scanning (Dhooge et al., 2005) could not demonstrate anomalies of the inner ear or vestibular system responsible for the hearing loss. Only one study showed hypoplastic lateral semicircular canals by CT-scanning in two TS patients with SNHL (Makishima et al., 2009).

The lack of endogenous estrogens has been proposed to be a contributing factor in the cause of SNHL (Hultcrantz et al., 2006). Estrogen receptors α and β have already been shown to exist in the human inner ear. Although there are indications that estrogens may have a beneficial effect on hearing, this requires further research (Hultcrantz et al., 2006; Stenberg et al., 2001). Concerning body height and serum IGF-1 concentrations, one study showed a positive correlation with hearing function (Barrenas et al., 2000).

The aim of this study was to determine the prevalence and features of ear and hearing problems in TS children and to correlate their audiometric data with different karyotypes. Finally, recommendations for the otologic care of TS children are given.

2. Materials and methods

2.1. Patients

The study was approved for by the medical ethical committee of the Radboud University Nijmegen Medical Centre (RUN MC). Between 2004 and 2008, 77 TS children under regular control of their pediatric endocrinologist received an invitation letter for otologic and audiologic screening. Sixty underwent screening and were included in this study. The mean age was 11.2 years (range 1.7–21.1) for otologic examination and 11.7 years (range 4.1–21.1) for audiologic examination. Because of their young age, 4 children were only tested with a screening test consisting of the head turn response to sound stimuli. Informed consent was obtained prior to participation. Medical history was taken, focusing on previous and current ear infections, hearing loss, karyotype and growth hormone and estrogen substitution therapy.

2.2. Otologic and audiologic examination

The otologic and audiometric data were retrieved from the medical files. We describe the findings at the time of everyone's last evaluation that was performed before the start of this study.

All ears were externally as well as microscopically examined. Hearing measurements were conducted according to standard audiometric methods (ISO 389) in a sound proof room. Pure tone hearing thresholds (dB hearing level, dB HL) were determined by air conduction (AC) and bone conduction (BC) for the following test frequencies: (0.25) 0.5, 1, 2, 4 and 8 kHz. As always, there can be a 5 dB machine error rate associated with audiogram measurement. Based on pure tone audiograms, different audiometric categories were developed in order to correlate audiometric findings to the underlying karyotype. The classification of audiometric categories as mentioned below was used as the different types of hearing impairment presented themselves in such a way.

2.2.1. Normal hearing

The AC thresholds were equal to or better than 20 dB HL across the frequency range of 0.25–8 kHz. When there was a dip within the normal range, the subject fell into the mid-frequency dip category (see below). Audiograms with an air-bone gap (ABG) of at least 10 dB at more than one frequency, within the normal range, were categorized as mild CHL (see below).

2.2.2. Mild conductive hearing loss

The AC thresholds were never worse than 20 dB HL, though there was an ABG of at least 10 dB at more than one frequency. By this classification we include this relevant ABGs in the analysis.

2.2.3. Conductive hearing loss (CHL)

AC thresholds were worse than 20 dB HL at one or more frequencies in the range of 0.25–8 kHz. There was an ABG of at least 10 dB at one or more frequencies at which the AC threshold was worse than 20 dB HL. BC thresholds were better than 20 dB HL at any frequency.

2.2.4. Mixed hearing loss (MHL)

The BC thresholds were worse than 20 dB HL at one or more frequencies in the range of 0.25–8 kHz and there was an ABG of at least 10 dB at one or more frequencies.

2.2.5. Pure sensorineural hearing loss (SNHL)

The AC thresholds were worse than 20 dB HL at one or more frequencies in the range of 0.25–8 kHz and there was no ABG. High-frequency SNHL was defined as AC thresholds worse than 20 dB HL at 4 kHz or higher frequencies or AC thresholds worse than 20 dB HL at frequencies below 4 kHz with an increasing loss with increasing frequency ('down sloping loss').

2.2.6. Sensorineural mid-frequency dip

This category included audiograms showing the typical mid-frequency dip within the range of 0.5–4 kHz. The dip was defined as BC thresholds being at least 10 dB HL worse (at one or two frequencies) than all of the lower and higher frequencies.

2.3. Statistical analysis

We tested the hypothesis that children with a monosomy or isochromosome have a higher occurrence of hearing problems compared to those with a mosaicism or structural chromosomal anomaly. First, we tested whether or not each type of hearing impairment (audiometric category) was distributed by chance alone over the different karyotypes. We used the chi-square test for the goodness of fit in a 2×3 table (degrees of freedom d.f. $= 2$). Fisher's exact test was performed in a 2×2 table on the monosomy and mosaicism groups, comparing the separate prevalence numbers of the right and left ear to test whether or not there was a significant difference between both ears.

Linear regression was used to analyze the influence of age and karyotype on hearing. An F test was used to compare between