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Otolaryngologic markers for the early diagnosis of Turner syndrome

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Abstract

Objective—To identify and characterize otolaryngologic markers for the early diagnosis of Turner Syndrome (TS).

Study Design—Prospective cohort survey.

Setting: Clinical Center of the National Institutes of Health (NIH).

Patients: Ninety-one females, 7 - 61 years old (average = 28.7 y), enrolled in a multidisciplinary study of karyotype-phenotype correlations in TS.

Main Outcome Measures: Age at diagnosis, X chromosome karyotype, history of chronic or recurrent otitis media (OM), sensorineural hearing loss (SNHL), palate dysmorphism, pinna deformity, pterygium colli, low posterior hairline, low-set ears, and micrognathia.

Results—Sixty-nine (76%) patients had a history of chronic or recurrent OM, 62 (68%) had a dysmorphic palate, 57 (63%) had SNHL, and 90 (99%) had one or more of these findings. 83 (91%; average age at diagnosis = 9.4 y) had one or more external craniofacial signs: pinna abnormalities, pterygium colli, low-set ears, micrognathia or a low posterior hairline. Eight patients (average age at diagnosis = 13.2 y) had no external craniofacial signs, although seven (88%) of these eight patients had a history of chronic or recurrent OM, dysmorphic palate or SNHL. The age at diagnosis was not significantly different between groups with or without external craniofacial signs ($P = 0.126$).

Conclusions—Patients with mild or incompletely penetrant TS phenotypes often present with otitis media, hearing loss, or both before the diagnosis of TS is established. Palatal dysmorphism, including ogival morphology, is another otolaryngologic marker for TS. Prompt recognition of these manifestations of TS could hasten its diagnosis and appropriate medical care.

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INTRODUCTION

Turner Syndrome (TS) affects up to one in 2000 live female births and is characterized by the total or partial loss of one X chromosome[1, 2]. Frequently observed manifestations of TS include short stature, lymphedema, gonadal dysgenesis, cardiovascular anomalies, renal abnormalities, hypertension, hypothyroidism, glucose intolerance and hyperlipidemia[1, 2]. Some of the features frequently encountered in the otolaryngology clinic are sensorineural hearing loss (SNHL)[3], recurrent otitis media (OM), pterygium colli and craniofacial dysmorphism[1, 2]. Commonly reported craniofacial findings include a low hairline, low-set ears, micrognathia, and oral palatal abnormalities[1, 2].

TS patients are thought to have an increased incidence of cleft palate[4-6]. Less morbid palatal morphologies are more common and include a narrow, high-arched or ogival (steeple-shaped) palate, or a combination of these morphologies[6-13]. The ogival palate may be inaccurately or incompletely described as high-arched or narrow[14], especially in the absence of cephalometric measurements. Similarly, prominent lateral ridges produce a different but distinctive palatal morphology that can also be mischaracterized as narrow or high-arched[11, 15]. Early diagnosis of TS is important for timely detection and surveillance of medically significant features such as congenital heart disease, and the prompt institution of therapies such as growth hormone, estrogen-progesterone and psychosocial counseling[1, 2]. Unfortunately, most girls with TS are not correctly diagnosed until age 10-12 when short stature and delayed pubertal development finally lead to cytogenetic testing[16]. However, many of these girls may present with distinctive otolaryngologic signs and symptoms prior to the diagnosis of TS. We sought to characterize the otolaryngologic manifestations of TS in order to facilitate its early detection in patients who may not have more obvious features.

SUBJECTS AND METHODS

Subjects

Ninety-one TS subjects with a wide spectrum of phenotypic severity were prospectively ascertained in a multidisciplinary study of genotype-phenotype correlations at the Clinical Center of the National Institute of Health (NIH). The average age at evaluation was 28.7 y (range = 7 - 61 y). The eligibility criteria comprised phenotypic characteristics of TS and karyotypic evidence of an X-chromosome abnormality with fewer than 30% normal cells on a 50-cell blood karyotype. Seventy-five subjects had monosomy X (45,X) and 16 had partial X monosomy comprising 46,X,delXp (n =2), 46,X,delXq (n = 2), 46,X,iXq (n = 5), and complex karyotypes including mosaics for 45,X and one of the above-mentioned X abnormalities (n = 7). Written informed consent was obtained from all subjects or parents of minor subjects. The study was approved by the Institutional Review Board of the National Institute for Child Health and Development, National Institutes of Health.

Clinical evaluation

Subjects or their parents completed a questionnaire about their past and present otolaryngologic signs and symptoms of TS. Their responses were reviewed and discussed within the context of a medical history interview and physical examination by an otolaryngologist-head and neck surgeon. Past medical records were evaluated when available. Dysmorphic features such as pinna and palate malformations were photo-documented. Palates were considered dysmorphic if they were high-arched, ogival, or had prominent lateral ridges resulting in the appearance of a narrow or high arch (Figure 1). High-resolution temporal bone CT scans were obtained for the first 14 subjects and reviewed by a Neuroradiologist and an Otolaryngologist-Head and Neck Surgeon. Cochlear height and lateral semicircular canal bony island width was measured on coronal and axial sections, respectively. Hypoplasia and hyperplasia were defined as

measurements outside normal ranges for cochlear height (4.4 - 5.9 mm) or lateral semicircular canal bony island width (2.6 - 4.8 mm)[17].

The results of pure-tone and speech audiometry, tympanometry and stapedial reflex testing are described elsewhere[3]. A history of chronic or recurrent OM was defined by report of one or more episodes. SNHL was defined by a bone conduction threshold ≥ 25 dB HL at any test frequency with or without an air-bone gap, and thus included those with mixed hearing loss.

Statistical analysis

We tested 2 × 2 associations among clinical variables and karyotypes by Fisher's Exact test. We compared average age at diagnosis by Student's *t*-test and Mann-Whitney test.

RESULTS

The average age at diagnosis was 9.7 y (range = 0 - 38 y). The average age at diagnosis was 9.2 y for monosomic 45,X and 12.0 y for partial X monosomic patients. This difference was not significant ($P = 0.197$).

Sixty-nine (76%) subjects had a history of OM, 57 (63%) had SNHL, 62 (68%) had a dysmorphic palate (Figure 1) and two (2%) had a history of cleft palate. Among subjects with SNHL, an isolated mid-frequency hearing loss was observed in four (7%) subjects and a mid-frequency hearing loss in combination with high frequency hearing loss was observed in 38 (60%) subjects. Forty-eight subjects (53%) had pinna abnormalities, 35 (38%) had pterygium colli, 66 (73%) had a low posterior hair line, 34 (37%) had low-set ears, and 22 (24%) had micrognathia. Dysmorphic palate, low posterior hairline, low-set ears, and micrognathia each showed a significant association with monosomy 45,X (Table 1). The presence of any one or more of the five external craniofacial signs did not show a significant association with monosomy 45,X ($P = 0.143$).

The average age at diagnosis was 9.4 y for patients with one or more external craniofacial signs in comparison to 13.2 y for subjects without any external craniofacial signs. This difference was not significant ($P = 0.687$). Seven (88%) of eight subjects without external craniofacial signs had OM, SNHL, or an abnormal palate (Table 2). We detected no significant association of OM, SNHL, or palate dysmorphism with the presence or absence of external craniofacial signs (Table 2).

Fourteen patients had normal CT scans of the temporal bones. One patient had evidence of chronic OM and a previous right tympanoplasty-mastoidectomy (not shown). We observed hypoplastic lateral semicircular canals (1 bilateral, 1 left) in two other patients, all of whom had SNHL (Figure 2). One of these patients also had a posterior dehiscence of the right superior semicircular canal with the posterior fossa but she had no history of vertigo. There was no association between the presence of vestibular dysmorphism and karyotype ($P > 0.5$).

DISCUSSION

Our comprehensive and prospective study design with stringent karyotype documentation should provide a description of the otolaryngologic manifestations of TS that is less biased than previous retrospective or referral-based studies. Nevertheless, our observed prevalence of palatal abnormalities in TS patients is consistent with previous reports[6-9, 11-13]. The high-arched palate has been emphasized as a clinical marker for the timely diagnosis of TS[12], although it can be a relatively common, nonspecific and subjective finding. Many palates that are qualitatively described as high-arched may actually be normal in height and more accurately described as narrow with prominent lateral ridges[11, 15]. An ogival or steeple-shaped palate

may be more specific for TS and is less common or prone to subjective judgment than "high-arched". There are reports of ogival palates noted in patients with Hutchinson-Gilford progeria[18] and Cornelia de Lange syndromes[19]; however these extremely rare entities are not usually in the differential diagnosis.

Our observed frequencies of chronic or recurrent otitis media and SNHL in TS are also consistent with previous reports[3, 20-22]. Almost all of our TS subjects, even individuals with no external craniofacial signs, had recurrent or chronic OM, SNHL or a dysmorphic palate. Any of these findings in combination with one another or other manifestations of TS in a female patient should alert the clinician to this possible diagnosis. This would facilitate earlier detection and management of the significant medical and psychological manifestations of this disorder.

CONCLUSION

Patients with mild or incompletely penetrant TS phenotypes often present with otitis media, hearing loss, or both before the diagnosis of TS is established. Palatal dysmorphism, especially ogival morphology, is a key otolaryngologic marker for TS. Prompt recognition of these manifestations of TS could hasten its diagnosis and appropriate medical care.

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References

1. Bondy CA. Care of girls and women with Turner syndrome: A guideline of the Turner Syndrome Study Group. J Clin Endocrinol Metab 2007;92:10–25. [PubMed: 17047017]
2. Frias JL, Davenport ML. Health supervision for children with Turner syndrome. Pediatrics 2003;111:692–702. [PubMed: 12612263]
3. King KA, Makishima T, Zalewski CK, et al. Analysis of auditory phenotype and karyotype in 200 females with Turner syndrome. Ear Hear 2007;28:831–841. [PubMed: 17982369]
4. Corona-Rivera JR, Corona-Rivera E, Bobadilla-Morales L, Garcia-Cobia TA, Corona-Rivera A. Cleft lip and/or palate in two cases of 46,X,i(Xq) Turner syndrome. Genet Couns 2002;13:19–22. [PubMed: 12017233]
5. Gorlin, RJ.; Cohen, MM., Jr.; Hennekam, RCM. Syndromes of the Head and Neck. Vol. 4th ed.. Oxford University Press; New York: 2001.
6. Lopez ME, Bazan C, Lorca IA, Chervonagura A. Oral and clinical characteristics of a group of patients with Turner syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002;94:196–204. [PubMed: 12221388]
7. Johnson R, Baghdady VS. Maximum palatal height in patients with Turner's syndrome. J Dent Res 1969;48:473–476. [PubMed: 5254490]
8. Laine T, Alvesalo L, Lammi S. Palatal dimensions in 45,X-females. J Craniofac Genet Dev Biol 1985;5:239–246. [PubMed: 4044787]
9. Lemli L, Smith DW. The Xo Syndrome. a Study of the Differentiated Phenotype in 25 Patients. J Pediatr 1963;63:577–588. [PubMed: 14074416]
10. Oberman JW. The prepuberal diagnosis of ovarian agenesis and its relationship to status Bonnevie-Ullrich. J Pediatr 1955;47:48–59. [PubMed: 14392553]
11. Perkiomaki MR, Alvesalo L. Palatine ridges and tongue position in Turner syndrome subjects. Eur J Orthod 2008;30:163–168. [PubMed: 18281708]
12. Savendahl L, Davenport ML. Delayed diagnoses of Turner's syndrome: proposed guidelines for change. J Pediatr 2000;137:455–459. [PubMed: 11035820]

13. Szilagyi A, Keszthelyi G, Nagy G, Madlena M. Oral manifestations of patients with Turner syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2000;89:577–584. [PubMed: 10807714]
14. Shapiro BL, Gorlin RJ, Redman RS, Bruhl HH. The palate and Down's syndrome. N Engl J Med 1967;276:1460–1463. [PubMed: 4226066]
15. Hanson JW, Smith DW, Cohen MM Jr. Prominent lateral palatine ridges: developmental and clinical relevance. J Pediatr 1976;89:54–58. [PubMed: 932903]
16. Stochholm K, Juul S, Juel K, Naeraa RW, Gravholt CH. Prevalence, incidence, diagnostic delay, and mortality in Turner syndrome. J Clin Endocrinol Metab 2006;91:3897–3902. [PubMed: 16849410]
17. Purcell DD, Fischbein NJ, Patel A, Johnson J, Lalwani AK. Two temporal bone computed tomography measurements increase recognition of malformations and predict sensorineural hearing loss. Laryngoscope 2006;116:1439–1446. [PubMed: 16885750]
18. Merideth MA, Gordon LB, Clauss S, et al. Phenotype and course of Hutchinson-Gilford progeria syndrome. N Engl J Med 2008;358:592–604. [PubMed: 18256394]
19. Grau Carbo J, Lopez Jimenez J, Gimenez Prats MJ, Sanchez Molins M. Cornelia de Lange syndrome: a case report. Med Oral Patol Oral Cir Bucal 2007;12:E445–448. [PubMed: 17909511]
20. Barrenas M, Landin-Wilhelmsen K, Hanson C. Ear and hearing in relation to genotype and growth in Turner syndrome. Hear Res 2000;144:21–28. [PubMed: 10831862]
21. Dhooge IJ, De Vel E, Verhoye C, Lemmerling M, Vinck B. Otologic disease in turner syndrome. Otol Neurotol 2005;26:145–150. [PubMed: 15793396]
22. Morimoto N, Tanaka T, Taiji H, et al. Hearing loss in Turner syndrome. J Pediatr 2006;149:697–701. [PubMed: 17095347]

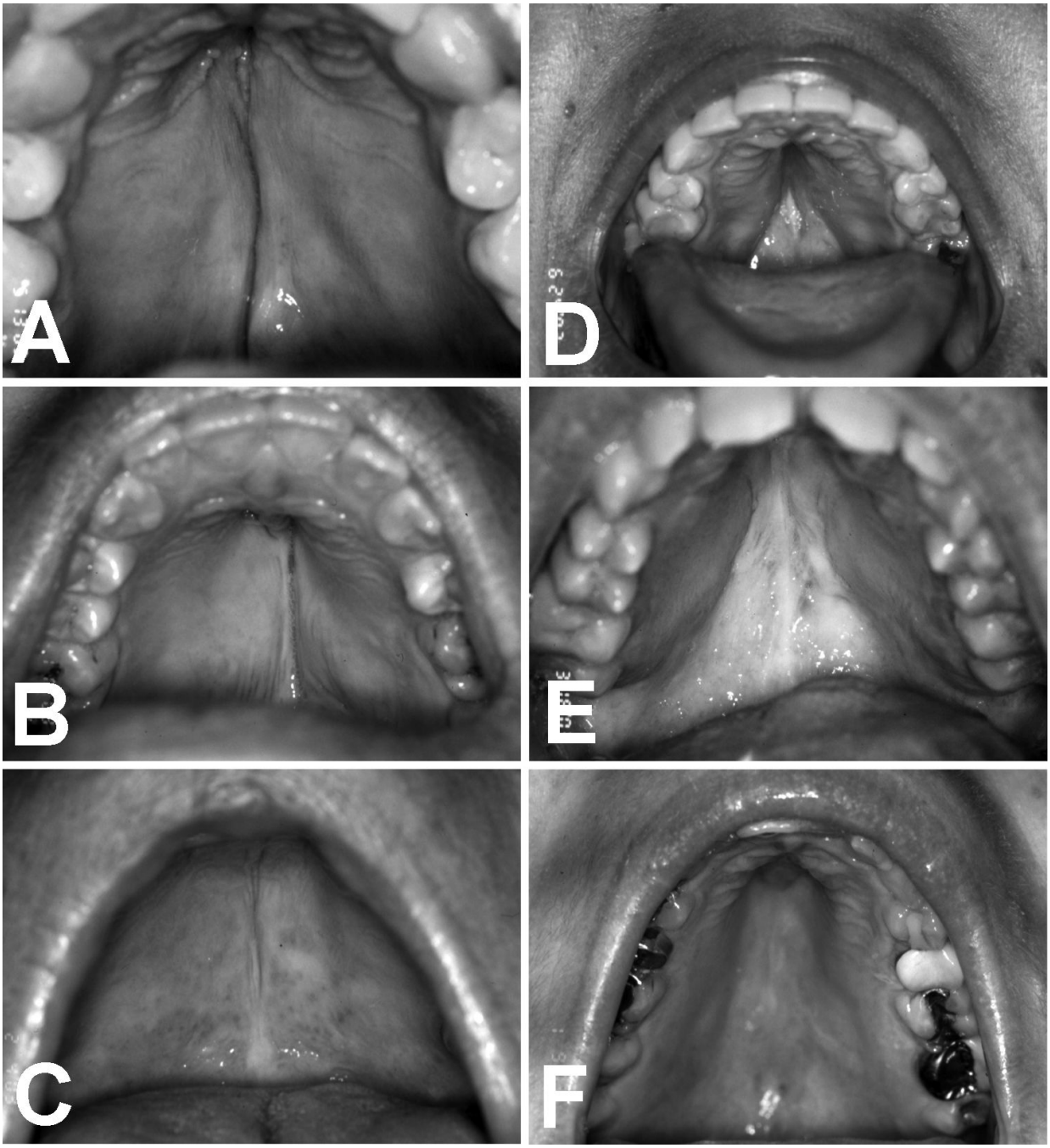

Figure 1.
Palate dysmorphism in TS includes ogival (steeple-shaped) morphology (A,B,C) and prominent lateral palatal ridges (D,E,F).

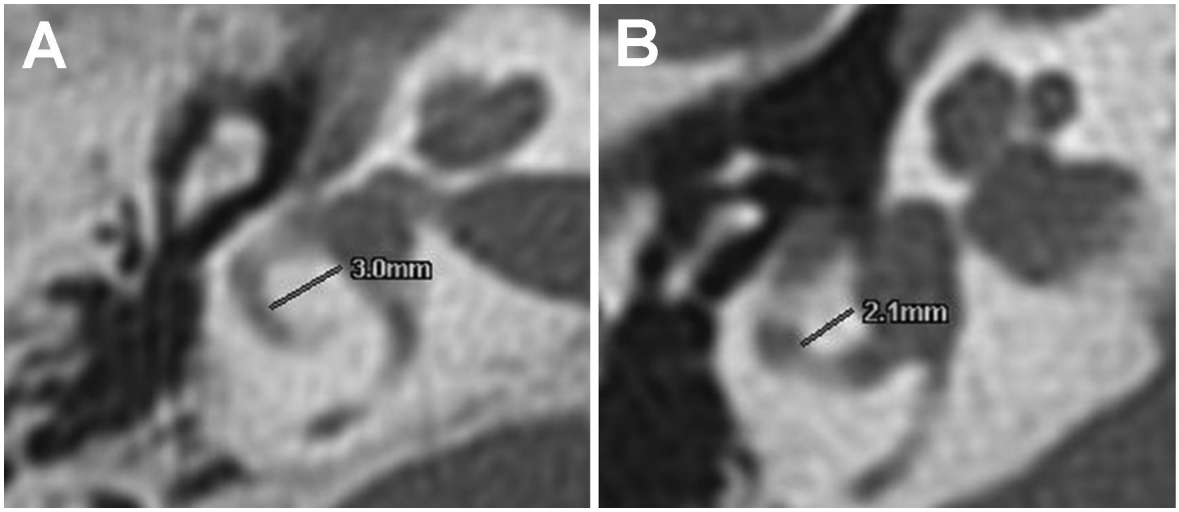

Figure 2.
CT scan images of normal (A) and hypoplastic (B) lateral semicircular canals. Lateral semicircular canal bony islands widths are indicated with lines and corresponding numerical measurements.

Table 1

Associations of Clinical Features with Karyotype

Clinical feature	No. of patients		*P* value[b]
	Monosomy X (45,X) (n=75)	Partial or mosaic monosomy X[a] (n=16)	
Otitis media (76%)	57	12	0.579
Low posterior hairline (73%)	58	8	0.031*
Dysmorphic palate (68%)	55	7	0.024*
Sensorineural hearing loss (63%)	50	7	0.077
Pinna deformity (53%)	39	9	0.488
Pterygium colli (38%)	32	3	0.063
Low-set ears (37%)	32	2	0.019*
Micrognathia (24%)	22	0	0.0073*
Any external signs[c](91%)	70	13	0.143

[a] includes: 46,X,delXp; 46,X,delXq; 46,X,iXq; and complex X karyotypes including mosaics for 45,X or one of these abnormal karyotypes.

[b] Fisher's exact test, two-tailed.

[c] pterygium colli, low posterior hairline, low-set ears, pinna deformity or micrognathia.

* statistically significant.

Table 2
Associations of Otolaryngologic Features with External Craniofacial Signs

Otolaryngologic feature	No. of patients with or without external craniofacial signs[a]		*P* value[b]
	With (n=83)	Without (n=8)	
Otitis media (OM), n=69 (76%)	64	5	0.296
Dysmorphic palate, n=62 (68%)	59	3	0.064
Sensorineural hearing loss (SNHL), n=57 (63%)	52	5	0.635
OM, SNHL or dysmorphic palate, n=90 (99%)	83	7	0.087

[a] pterygium colli, low hairline, low-set ears, pinna deformity or micrognathia.

[b] Fisher's exact test, two-tailed.