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Stylohyoid Ligament Calcification: A Greater-Than-Expected Cause of Otalgia in Turner Syndrome

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Context: Otitis is common in patients with Turner syndrome (TS) and may be misdiagnosed in the presence of other causes of otalgia.

Objective: We hypothesized that stylohyoid ligament calcification (SLC), named Eagle syndrome (ES), is a common cause of otalgia in TS.

Design: Cohort of 1-year data collection.

Setting: We analyzed all consecutive women with Turner syndrome (TW).

Patients: Ninety-six TW and 55 age-paired normal control women (CW).

Intervention: Participants were asked about current or past otalgia and had bilateral tonsillar palatine palpated by the same physician.

Main Outcome Measures: When otalgia or cervicalgia plus painful palatine tonsil palpation was positive, participants underwent facial X-ray or three-dimensional cranial CT. If SLC was >25 mm, ES was confirmed.

Results: Thirty-four TW (35%) had clinical signs and 27/34 (79%) had radiologically confirmed ES. Of the TW with confirmed ES (27/96; 28%), 14 (51.9%) were inadvertently treated for recurrent otitis as a presumed cause of otalgia. Eleven of the TW with ES (26.1%) were below age 21. There was no association with karyotype, age, body mass index, or growth hormone use. Ten CW (18.2%) complained of symptoms of ES, but only 4 (7.3%) were radiologically confirmed (CW vs TW, $P < 0.01$), and none were <21 years old. ES occurred more at younger ages in TW ($P < 0.002$).

Conclusion: ES is more prevalent in TW than in controls and occurs at younger ages. ES must be assessed as a common comorbidity of TS at any age, especially during childhood, as a differential diagnosis of otalgia.

Freeform/Key Words: Turner syndrome, otalgia, stylohyoid ligament, calcification, Eagle syndrome, otitis

Abbreviations: 3D, three-dimensional; CW, control women; ES, Eagle syndrome; SHL, stylohyoid ligament; SLC, stylohyoid ligament calcification; TS, Turner syndrome; TW, women with Turner syndrome; UNIFESP, Universidade Federal de São Paulo.

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Turner syndrome (TS) is genetically characterized by a partial or total loss of the second sex chromosome and has a postnatal incidence of 42 per 100,000 live-born girls [1–3]. In general, patients with TS present with increased morbimortality [1, 4]. The Turner Syndrome Consensus Study Group aims to consider TS and the karyotype in any girl with unexplained growth failure or pubertal delay or any constellation of typical clinical findings, including chronic otitis media [1, 5].

In childhood, girls with TS often suffer from repeated acute otitis media, and later in life they often complain of rapid-onset hearing problems due to sensorineural hearing impairment. In 325 women with TS, 61% had otitis, and 50% had an outer malformation of the ears [6]. Otitis episodes are more common in childhood, beginning early in life [7, 8].

In contrast, Eagle syndrome (ES), or stylohyoid ligament calcification (SLC) syndrome, is defined as the symptomatic elongation of the styloid process with mineralization of the stylohyoid ligament (SHL) complex [7]. ES is a frequently missed cause of chronic facial and cervical pain, sometimes radiating to the ear and often in an unremitting pattern [9]. The ossification of the SHL compresses and stretches the nerve structures (trigeminal, facial, glossopharyngeal, and vagus), producing pain [10]. Although 4% to 7.5% of the general population has anatomic alterations of the SHL, usually bilateral, only 4% to 10.3% of these patients experience pain [11–13].

In recent years, we have assisted women with Turner syndrome (TW) with a long-standing history of ear pain from childhood that was commonly treated as otitis with no improvement in pain. We hypothesized that ES could be a common cause of otalgia in TS separate from nonsuppurative otitis.

1. Subjects and Methods

A. Subjects

We performed a cross-sectional study from July 2013 to June 2015 by recruiting 104 consecutive TW in regular follow-up at the Endocrine Outpatient Clinic of Hospital São Paulo, Escola Paulista de Medicina, at the Universidade Federal de São Paulo (UNIFESP). The Research Ethics Committee of UNIFESP approved and registered the study (no. 16516413). A TS diagnosis was established based on clinical symptoms and confirmed by karyotype analysis according to the guidelines of the Turner Syndrome Consensus Study Group [5]. Seven patients were either lost to follow-up or gave up on participating in the study. Control women (CW) including companions, relatives, coworkers, and graduate students were invited to participate. All participants or their legal guardians, when necessary, signed the informed consent document. All participants were questioned about cervicalgia and otalgia and then underwent intraoral examination and palpation of palatine tonsils.

B. Imaging Studies

When either tonsillar fossa palpation upon physical examination or spontaneous pain of the mandibular and cervical region was positive, each subject underwent facial anteroposterior and lateral X-ray imaging. The SHL was radiographically evaluated by measuring the distance from its cranial base down to the osseous tip of each mandibular process. Scan images showing continuous or targeted calcification of the SHL >25 mm in length or bigger than a third of the subject's mandible height were considered altered and confirmed as abnormal SLC [14]. The same examiner performed all measurements. If the X-ray scan was not conclusive, then the subject was submitted to cranial and cervical CT with three-dimensional (3D) reconstruction of the SHL anatomical area, which was considered altered if the ligament calcification was >25 mm (SLC positive) [15]. Tomographic images were taken by a 64-channel Philips Brilliance with 01 × 01 mm multislice cuts with Bone Reconstruction 3d Stand B Bone Filter Detail.

C. Statistical Analysis

Data were presented as the mean ± SD for numeric variables and by a number and percentage for qualitative variables. Comparison of means was performed via Student unpaired *t* test. Kolmogorov-Smirnov tests were used to check for a normal population distribution. The contingency tables were used to determine whether the distribution of each group was contingent on the category in which it fell, and a Fisher exact test was applied.

2. Results

Ninety-six TW were evaluated, and one was excluded because she did not complete the evaluation. Their mean age was 23.1 ± 11.2 years, ranging from 3 to 64 years. Of these participants, 42 (43.8%) were <21 years old. Of all TW, 34/96 (35%) complained of symptoms and signs of ES, such as odynophagia, otalgia or cervicalgia, or painful palatine pillar on palpation, and 27/34 (79%) had the ES diagnosis radiologically confirmed, and thus 28% (27/96) of TW had confirmed ES. Representative ES radiological findings are depicted in Fig. 1. A significantly greater proportion of TW with ES were younger: 11 of the TW with ES were below age 21 (11/34, 78%), yet all CW with ES were >30 years old ($P < 0.05$). In TW, there were no associations between ES and karyotype, age, body mass index, use or duration of growth hormone, or other comorbidities, as shown in Table 1. Of the 27 patients with confirmed ES, 14 (51.9%) had a history of otalgia or recurrent otitis. In all, palpation of the tip of the styloid process exacerbated the symptoms and suggested ES.

Fifty-nine CW were systematically evaluated, but four were excluded because of incomplete assessments. The CW group had a mean age of 34.7 ± 16.2 years, from 7 to 70 years. Fifteen (27.3%) were below age 21, but none had confirmed ES. The youngest CW with ES was 31 years. Ten CW (18.2%) presented with ES symptoms, although only 4 (7.3%) had the diagnosis confirmed.

All subjects enrolled in this study, both TW and CW, denied trauma, radiation therapy, or any intense manipulation of the cervical or mandibular areas. Comparing TW and CW groups, there was a significantly higher frequency of ES in TW compared with CW ($P < 0.01$), as shown in Table 1. Furthermore, ES occurred more at younger ages in TW than in CW ($P < 0.002$).

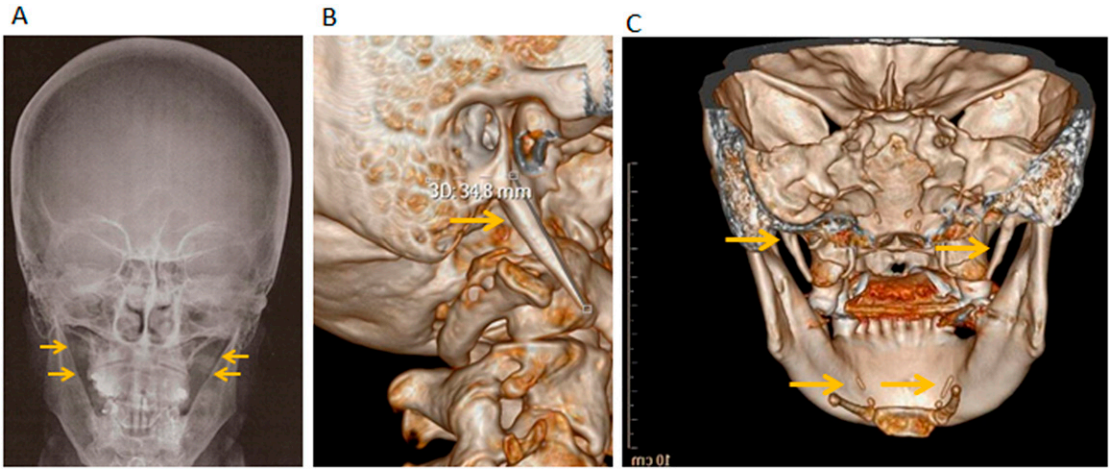

Figure 1. Representative radiological findings showing calcification of the SHL in different patients with TS. Arrows identify the prolonged and calcified SHL. The standard measure of SHL is <25 mm. (A) Frontal cranial simple X-ray showing an SHL >40 mm. (B) 3D CT sagittal cranial view evidencing an SHL of 34.8 mm. (C) Frontal cranial CT showing an SHL of 29 mm on the right and 23 mm on the left side.

Table 1. Summary of Clinical Data From TW and CW With and Without ES

	TW			CW			
	Total	**ES−**	**ES+**	**Total**	**ES−**	**ES+**	***P***
n (%)	96	69 (72)	27 (28)	55	51 (93)	4 (7)	<0.01
Age, y	23.1 ± 11.2	22.6 ± 5.5	24.5 ± 8.2	34.7 ± 16.2	34.4 ± 16.7	38.0 ± 7.0	ns
Body mass index, kg/m^2	24.0 ± 5.7	24.2 ± 5.6	23.4 ± 6.1		-		ns
GH use, %	57 (59)	41 (59)	16 (59)				ns
Duration of GH use, mo	37.3 ± 24.7	36.4 ± 24.7	38.5 ± 25.6				ns
Type 2 diabetes or glucose intolerance, n (%)	5 (5)	3 (4)	2 (7)	5 (10)	5 (10)	0	ns
Systemic arterial hypertension, n (%)	10 (10)	7 (10)	3 (9)	9 (16)	8 (16)	1 (25)	ns
Obese or overweight, n (%)	28 (28)	24 (35)	4 (15)	26 (47)	25 (48)	1 (25)	ns
Dyslipidemia, n (%)	15 (15)	8 (11)	6 (22)	6 (11)	6 (12)	0	ns
Osteoporosis, n (%)	25 (24)	12 (17)	13 (48)	1 (2)	1	—	—

Abbreviation: ns, not significant.

3. Discussion

We observed that symptomatic calcification of the SHL >2.5 cm is more common in TW compared with CW in our study. More than a quarter of the TW population below age 21 had the ES diagnosis radiologically confirmed. ES diagnosis was often related to otalgia or cervicalgia in more than half of patients with TS.

Regarding cranial abnormalities in TW, the calvarium, maxilla, and mandible are smaller and the cranial base is shorter and flattened [16]. An ogival palate and small teeth with poor occlusion are also described [17]. Otitis media is commonly related to TS and known as a result of low ear implantation, usually occurring for a longer period in TS than among children prone to recurrent otitis [6]. Indeed, some girls of short stature were diagnosed with TS as a result of recurrent otitis media [8]. In our cross-sectional research, 52% of TW with confirmed ES had frequent and persistent otalgia.

The calcified SHL and an elongated styloid process can be radiographically identified, and although the panoramic oral X-ray is easily assessed, it is prone to frequent errors [18]. When simple X-ray is not conclusive, 3D CT is the method of choice for confirming ES diagnosis [19, 20].

The symptoms can be confused with a wide variety of facial neuralgias and oral and temporomandibular joint diseases [21]. Most cases are related to a history of trauma, amygdalate inflammation, and genetic syndromes related to precocious aging [22, 23]. In fact, patients with ES usually have a long history of chronic pain treated by multiple physicians [24].

If not related to trauma or local radiotherapy, the exact cause of the styloid process elongation due to calcification and subsequent ossification of the ligament is unclear. It has been speculated that it may be related to variations in the development of Reichert's cartilage during embryogenesis or may be determined genetically [25, 26]. Various hypotheses have been proposed, such as the theory of reactive metaplasia, reactive hyperplasia, anatomic variance secondary to aging, developmental anomaly, or trauma leading to simulating tendinosis due to loss of elasticity of the SHL [27].

ES incidence varies from 1.4% to 83% depending on the assessment method and applied criteria [19]. In general, it is usually accepted as 3.3%, but the incidence is growing, with increased elongation with age and female preponderance [28]. By indirect observation of the routine digital panoramic radiography evaluation of asymptomatic Brazilian subjects, no alterations were found before the age of 18 [29]. In another Brazilian study that used the same diagnostic criteria as in this study, a 15% frequency of calcification of the SHL was observed more often in older women population, and no subjects were <18 years old [30].

Including ES in the differential diagnosis is very important because it has a specific type of treatment, and distinguishing ES from chronic otitis may help prevent the mistaken use of antibiotics. In ES cases without symptomatic pain relief, surgical treatment may be indicated [31, 32].

In conclusion, a diagnosis of ES is more prevalent in TW than in CW, and it occurs at a younger age. It is an important differential diagnosis when evaluating cervicalgia, otalgia, or otitis in TS throughout life, especially in childhood. ES must be highlighted as a common comorbidity in TS.

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Data Availability: The data sets generated or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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