Styloid Process Elongation on Cervical Spine Computed Tomography is Associated with the Enthesopathy-Related Diseases in Ankylosing Spondylitis and Diffuse Idiopathic Skeletal Hyperostosis

Talia Levy[1], Salim Bader[1], Kay-Geert Hermann MD[3], Gal Yaniv MD[1], Gahl Grinberg MD[1], Oshry Mozes MD[1], Merav Lidar MD[2] and Iris Eshed MD[1]

[1]Department of Diagnostic Imaging and [2]Rheumatology Unit, Sheba Medical Center, Tel Hashomer, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[3]Department of Radiology, Charité Medical School, Berlin, Germany

ABSTRACT: **Background:** Enthesopathy may lead to calcification of the stylohyoid ligament and can cause elongation of the styloid process (SP).

Objectives: To evaluate whether SP elongation is associated with two common enthesitis-related diseases: ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH).

Methods: Cervical spine computed tomography (CT) examinations of patients with DISH (n=64, Resnick criteria), AS (n=24, New York criteria) and controls (no radiological signs of DISH or AS, n=54) were retrospectively evaluated. The length of right and left SP was measured independently by two readers on coronal and sagittal curved reformats. The average right and left styloid length and average length per person were compared among the groups.

Results: Demographic characteristics were similar between the DISH and control groups (average age 68.2 ± 15.7, 69.2 ± 12.7 years, male:female ratio 48:16 and 35:19, respectively, $P > 0.05$), whereas age was significantly lower (average age: 53 ± 15 years, $P < 0.0001$) in the AS group, which was also composed mainly of men. The AS and DISH groups had significantly longer SP compared to controls (AS 37.9 ± 9.6 mm, DISH 34.4 ± 9 mm, control 30.3 ± 10.1 mm, $P < 0.05$). There was no correlation between age and SP length. Inter-reader reliability of SP measurements was excellent in all groups (ICC = 0.998, $P < 0.0001$).

Conclusions: SP elongation is associated with both AS and DISH substantiating the enthesopathy-related pathophysiology of this finding.

IMAJ 2017; 19: 670–673

KEY WORDS: styloid process (SP), ankylosing spondylitis (AS), diffuse idiopathic skeletal hyperostosis (DISH), enthesitis, computed tomography (CT), cervical spine

The styloid process (SP), bilateral, long, and thin osseous extension of the temporal bone, is connected to the hyoid bone by the stylohyoid ligament [1,2]. Ossification or calcification of the stylohyoid ligament can cause elongation of the SP [3,4], which may cause a rare condition of craniofacial and cervical pain, termed Eagle syndrome [5]. The average length of the SP in an adult is 20 to 30 mm, and it is considered elongated when it exceeds 40 mm in length [6,7].

The pathogenesis of SP elongation is unclear but a potential explanation may be repetitive micro-trauma causing enthesopathy and ossification of the stylohyoid ligament at its insertion on the SP [8].

Enthesitis, defined as inflammation at the attachment site of a tendon or a ligament to bone, is a key feature of the spondyloarthropathies [9,10] of which ankylosing spondylitis (AS) is the prototype. AS typically targets the axial skeleton and sacroiliac joints but may also involve entheseal sites, peripheral joints, skin, eyes, and bowel [11]. In accordance with the hypothesis of an underlying enthesopathy contributing to SP elongation, the SP of AS patients was shown to be longer than those of controls when measured on lateral cervical radiogrpahs [8].

Diffuse idiopathic skeletal hyperostosis (DISH) is an additional disease, which is characterized by robust ossification and calcification of the peripheral entheses [12,13]. The hallmark of the disease is right-sided anterolateral ossification, bridging at least four contiguous vertebrae of the thoracic spine14]]. It has been postulated, but not verified, that DISH may be associated with SP elongation and Eagle syndrome, in a way similar to AS [15,16].

The objective of the current study was to evaluate whether SP elongation, postulated to occur as the result of enthesopathy, is associated with AS and DISH, and whether SP elongation may aid in differentiating between these two entities

PATIENTS AND METHODS

Institutional review board approval for the review of clinical files and cervical spine computed tomography (CT)

This work was presented at a radiology–rheumatology meeting focusing on the contribution of imaging to the understanding of the pathogenesis and treatment decisions in musculoskeletal rheumatic diseases that took place in December 2016 at the Sheba Medical Center, Tel Hashomer, Israel

examinations of AS, DISH, and control patients was obtained. Informed consent was waived due to the retrospective nature of the study.

PATIENTS

Archived records of 300 subjects with a radiologic diagnosis of DISH (Resnick criteria [14]) and 120 patients with AS (New York criteria [17]) were retrieved. The institution's picture archiving and communication system (PACS) was cross-matched for the subjects who had had a cervical CT examination. Subjects with DISH or AS who had undergone a cervical CT composed the study group.

Subjects who had undergone a CT examination of the entire spine in which no evidence of DISH or AS, as per radiologic criteria, was present, composed the control group. Explicitly, subjects with three or more flowing osteophytes who had syndesmophytes, and/or sacroiliac joint changes compatible with either DISH or AS were excluded from the control group.

CT examinations of the cervical spine of subjects with DISH (n=64; 48 males, 16 females, mean age 68.7 ± 15 years), AS (n=24; 22 males, 2 females, mean age 53 ± 15 years) and controls (n=54; 35 males, 19 females, mean age 69.2 ± 13 years) were retrospectively evaluated.

CT TECHNIQUE AND SP MEASUREMENTS

All CT studies were performed using the following CT scanners: M×8000 Quad 4-slices, M×8000 IDT 16-slices, Brilliance 40, 64 and 128 (Philips Medical Systems, Eindhoven, The Netherlands) and 64-slice VCT LightSpeed (GE Medical Systems, Milwaukee, WI, USA). Slice thickness ranged from 0.6 to 2.5 mm. A multiplanar curved reformat along the right and left styloid process were constructed in the coronal and sagittal planes to evaluate its length.

The entire osseous length of the right and left SP from its base in the temporal bone was measured independently by two readers, blinded to the patient's clinical data and group association, in all three groups on the coronal and sagittal curved reformats [Figure 1]. The average of the coronal and sagittal measurements on either side was considered the actual SP length of that side. An average SP length per person (the average of the calculated SP length of each side) was also calculated.

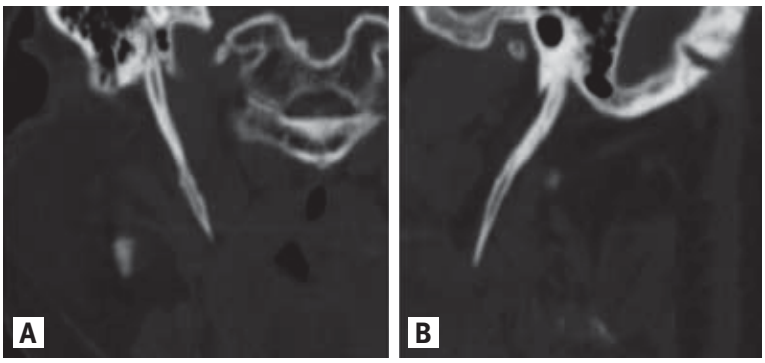
An elongated SP was defined as ≥ 40 mm in length [6,7]. The percentage of subjects with an elongated SP was compared among groups.

STATISTICAL ANALYSIS

After testing for normal distribution, a Student's *t*-test was used to compare the average right and left styloid length and average length among groups.

The DISH group was further divided into patients with or without cervical involvement, that is, ≥ 3 flowing osteophytes in the cervical spine.

Figure 1. Coronal **[A]** and sagittal **[B]** curved reformates of an elongated styloid process



Analysis was also performed in these two DISH subgroups as well as the AS and control groups.

Pearson's correlation was used to calculate correlation between SP length and age in each group.

Intraclass correlation coefficients (ICCs) were calculated using an analysis of variance (ANOVA) two-way random for absolute agreement of measurements between the two readers. *P*-values < 0.05 were considered to be statistically significant. ICC values were interpreted as follows: 0–0.2 = poor agreement, 0.3–0.4 = fair agreement, 0.5–0.6 = moderate agreement, 0.7–0.8 = strong agreement, and > 0.8 = almost perfect agreement. The percentage of both intra-and inter-observer agreement is also reported.

RESULTS

Age and gender distribution were similar between the DISH and control groups (average age 68.2 ± 15.7 and 69.2 ± 12.7 years, male/female ratio 48:16 and 35:19, respectively, $P > 0.05$) while significantly younger (average age 53 ± 15 years, $P < 0.0001$) patients as well as males were the predominate subjects in the AS group.

After checking for normal distribution, one patient in the control group, a 73 year old male, had an exceedingly long SP bilaterally (right: 72 mm, left: 94 mm). However, even on re-evaluation of the patient's CT examination and clinical file, no spinal or extra-spinal characteristics of DISH or AS, and no clinical complaints compatible with Eagle's syndrome were found. Since this was the only patient with an SP length longer than two standard deviations of the average SP length, this patient's results were excluded from the statistical analysis of the control group resulting in a group of 53 subjects.

SP lengths of the DISH, AS and control groups are presented in Table 1.

Although longer, the average AS SP length was not significantly different from the DISH average SP length ($P = 0.15$).

Both the AS and the DISH groups had a significantly longer average SP length compared to the controls (AS: $P = 0.02$,

Table 1. Average length (mm) of the styloid process (range) in the AS, DISH, and control groups

	AS (n=24)	DISH (n=64)	Control (n=53)
Right	38.1* (17.6–62.0)	34.1** (11.5–72.9)	30.5 (8.3–50.0)
Left	37.8* (17.3–57.7)	34.7** (22.3–61.8)	30.1 (8.9–52.9)
Average	37.9*	34.4**	30.3

AS = ankylosing spondylitis, DISH = diffuse idiopathic skeletal hyperostosis
*P = 0.02 (between AS and controls), **P = 0.01 (between DISH and controls)

DISH: P = 0.01). A significantly higher percentage of patients with AS (30%) and DISH (25%) had an elongated SP (≥ 40 mm) compared to the control group (9%).

Within the DISH subgroup, the presence of DISH in the cervical spine did not significantly affect the average SP length (34.1 mm vs. 34.5 mm in subjects with and without involvement of DISH in the cervical spine. respectively).

There was no correlation (based on Pearson's) between SP length and age in the AS, DISH, or control groups.

Inter-reader reliability of SP measurements was excellent in all groups (ICC: coronal = 0.991, $P < 0.0001$, sagittal = 0.999, $P < 0.0001$).

DISCUSSION

DISH and AS are both characterized by ossification of ligaments and tendons as well as enthesopathy in the axial and peripheral skeleton [18].

In the current study, as hypothesized, the length of the SP in patients with AS and DISH was significantly longer compared to control subjects.

SP length of AS patients as well as psoriatic arthritis patients was previously reported as longer than that of healthy controls on lateral cervical spine radiographs [8], corroborating our present findings. However, a previous study comparing the SP length on cervical CT scans of DISH vs. non-DISH subjects found no statistical difference in the two groups [16]. The cause of this apparent discrepancy is in the different methods used in the two studies. In the original study, performed more than 20 years ago, CT slices were thicker than those obtained today (mostly 5 mm) and the SP length was indirectly measured by counting the amount of consecutive slices in which it appeared. Presently, SP length is measured directly on angulated reformates undoubtedly resulting in a far more accurate value, which establishes the longer SP of DISH subjects.

There are several hypotheses attempting to explain SP elongation, including response to local chronic irritation, either mechanical or inflammatory, leading to enthesopathy at the SP–stylohyoid ligament enthesis [8], metabolic or endocrine disorders that cause ectopic calcification [19], and anatomic variants [20].

Both AS and DISH have known associations with enthesopathy, potentially supporting the local irritation-enthesopathy hypothesis.

Enthesopathy in AS patients is of an inflammatory nature [21], whereas its pathogenesis in DISH is not completely understood. Mechanical or degenerative causes were classically attributed to DISH enthesopathy. Recently a potential pathogenetic role of subclinical inflammation as well as metabolic syndrome were also suggested in DISH [12,22], potentially linking the two hypotheses for SP elongation (enthesopathy and metabolic) together in the same disease. The difference in lengths of SP between AS and DISH, although not statistically significant, may be indicative of the different pathogenic processes leading to its elongation resulting in a longer calcification/ossification segment in the AS group compared to the DISH group. The difference in SP length among the three groups (DISH, AS, and controls), unfortunately cannot be used to differentiate in them, especially due to the relatively wide length range and overlaps in the groups; however, when an elongated SP is observed, one should look for possible underling enthesopathic disease, such as DISH or AS.

The study's main limitations include the relatively small number of patients as well as the lack of relevant clinical data. However, the statistical significance calculated in thus small cohort indicates that the difference in SP length between the AS, DISH, and the control group is indeed significant.

Although the findings of the present study are not robust enough to warrant a recommendation of cervical spine CTs for patients suspected of having AS or DISH, they nonetheless highlight a significant radiological finding that is readily apparent on scans performed in these patients, most commonly for the evaluation of neck pain, which may facilitate an earlier diagnosis of these two, notoriously late-diagnosed entities. The importance of securing an early diagnosis for AS in the era of biologic therapy is obvious as patients who are diagnosed earlier have shown to have better functional outcomes compared to historic controls [23], and there is also initial data showing that bone formation is attenuated in animal models of disease [24]. As for DISH, timely diagnosis may allow for better control of the metabolic syndrome from which these patients frequently suffer, thus potentially lowering the risk of future stroke and coronary events. Moreover, both entities may be complicated by osteoporotic spines with a high risk of minor-trauma fractures [25], highlighting the need for early diagnosis, prevention and intervention.

CONCLUSIONS

In conclusion, SP elongation is seen more frequently in patients with AS and DISH, implying an enthesopathy-related pathogenesis. The difference in length between DISH and AS subjects suggests that enthesitis is driven by different mechanisms in each of the diseases.

Correspondence
Dr. I. Eshed
Dept. Diagnostic Imaging, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: (972-3) 530-2498
Fax: (972-3) 530-2220
email: iriseshed@gmail.com

References

1. Kaufman SM, Elzay RP, Irish EF. Styloid process variation. Radiologic and clinical study. *Arch Otolaryngol* 1970; 91 (5): 460-3.
2. Alpoz E, Akar GC, Celik S, Govsa F, Lomcali G. Prevalence and pattern of stylohyoid chain complex patterns detected by panoramic radiographs among Turkish population. *Surg Radiol Anat* 2014; 36 (1): 39-46.
3. Camarda AJ, Deschamps C, Forest D. Stylohyoid chain ossification: a discussion of etiology. *Oral Surg Oral Med Oral Pathol* 1989; 67 (5): 508-14.
4. Omnell KA, Gandhi C, Omnell ML. Ossification of the human stylohyoid ligament: a longitudinal study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998; 85 (2): 226-32.
5. Costantinides F, Vidoni G, Bodin C, Di Lenarda R. Eagle's syndrome: signs and symptoms. *Cranio* 2013; 31 (1): 56-60.
6. Gokce C, Sisman Y, Ertas ET, Akgunlu F, Ozturk A. Prevalence of styloid process elongation on panoramic radiography in the Turkey population from cappadocia region. *Eur J Den* 2008;2 (1): 18-22.
7. Gozil R, Yener N, Calguner E, Arac M, Tunc E, Bahcelioglu M. Morphological characteristics of styloid process evaluated by computerized axial tomography. *Ann Anat* 2001; 183 (6): 527-35.
8. Unlu Z, Tarhan S, Gunduz K, Goktan C. Relationship between ossification of the stylohyoid ligament and enthesopathy: a comparative study. *Clin Exp Rheumatol* 2002; 20 (5): 661-7.
9. Benjamin M, McGonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. *J Anat* 2001; 199 (Pt 5): 503-26.
10. Olivieri I, Barozzi L, Padula A. Enthesiopathy: clinical manifestations, imaging and treatment. *Baillieres Clin Rheumatol* 1998; 12 (4): 665-81.
11. Ghasemi-Rad M, Attaya H, Lesha E, et al. Ankylosing spondylitis: A state of the art factual backbone. *World J Radiol* 2015; 7 (9): 236-52.
12. Mader R, Verlaan JJ, Buskila D. Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms. *Nat Rev Rheumatol* 2013; 9 (12): 741-50.
13. Slonimsky E, Leibushor N, Aharoni D, Lidar M, Eshed I. Pelvic enthesopathy on CT is significantly more prevalent in patients with diffuse idiopathic skeletal hyperostosis (DISH) compared with matched control patients. *Clin Rheumatol* 2016; 35 (7): 1823-7.
14. Resnick D, Niwayama G. Radiographic and pathologic features of spinal involvement in diffuse idiopathic skeletal hyperostosis (DISH). *Radiology* 1976; 119 (3): 559-68.
15. Unlu Z, Orguc S, Eskiizmir G, Aslan A, Bayindir P. Elongated styloid process and cervical spondylosis. *Clin Med Case Rep* 2008; 1: 57-64.
16. Guo B, Jaovisidha S, Sartoris DJ, et al. Correlation between ossification of the stylohyoid ligament and osteophytes of the cervical spine. *J Rheumatol* 1997; 24 (8): 1575-81.
17. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984; 27 (4): 361-8.
18. Olivieri I, D'Angelo S, Palazzi C, Padula A, Mader R, Khan MA. Diffuse idiopathic skeletal hyperostosis: differentiation from ankylosing spondylitis. Curr *Rheumatol Rep* 2009; 11 (5): 321-8.
19. 19. Gokce C, Sisman Y, Sipahioglu M. Styloid process elongation or Eagle's syndrome: is there any role for ectopic calcification? *Eur J Dent* 2008; 2 (3): 224-8.
20. Krennmair G, Piehslinger E. Variants of ossification in the stylohyoid chain. *Cranio* 2003; 21 (1): 31-7.
21. McGonagle D, Khan MA, Marzo-Ortega H, O'Connor P, Gibbon W, Emery P. Enthesitis in spondyloarthropathy. *Curr Opin Rheumatol* 1999; 11 (4): 244-50.
22. Mader R, Novofestovski I, Adawi M, Lavi I. Metabolic syndrome and cardiovascular risk in patients with diffuse idiopathic skeletal hyperostosis. *Semin Arthritis Rheum* 2009; 38 (5): 361-5.
23. Huscher D, Thiele K, Rudwaleit M, et al. Trends in treatment and outcomes of ankylosing spondylitis in outpatient rheumatological care in Germany between 2000 and 2012. *RMD Open* 2015; 1 (1): e000033.
24. Tseng HW, Pitt ME, Glant TT, et al. Inflammation-driven bone formation in a mouse model of ankylosing spondylitis: sequential not parallel processes. *Arthritis Res Ther* 2016; 18: 35.
25. Yunoki M, Suzuki K, Uneda A, Okubo S, Hirashita K, Yoshino K. The importance of recognizing diffuse idiopathic skeletal hyperostosis for neurosurgeons: a review. *Neurol Med Chir (Tokyo)* 2016; 56 (8): 510-5.

Capsule

Staphylococcus aureus and *Staphylococcus epidermidis* strain diversity underlying pediatric atopic dermatitis

The heterogeneous course, severity, and treatment responses among patients with atopic dermatitis (AD; eczema) highlight the complexity of this multi-factorial disease. Earlier studies used traditional typing methods on cultivated isolates or sequenced a bacterial marker gene to study the skin microbial communities of AD patients. Shotgun metagenomic sequence analysis provides much greater resolution, elucidating multiple levels of microbial community assembly ranging from kingdom to species and strain-level diversification. Byrd et al. analyzed microbial temporal dynamics from a cohort of pediatric AD patients sampled throughout the disease course. Species-level investigation of AD flares showed greater *Staphylococcus aureus* predominance in patients with more severe disease and *Staphylococcus epidermidis* predominance in patients with less severe disease. At the strain level, metagenomic sequencing analyses demonstrated clonal *S. aureus* strains in more severe patients and heterogeneous *S. epidermidis* strain communities in all patients. To investigate strain-level biological effects of *S. aureus*, the authors topically colonized mice with human strains isolated from AD patients and controls. This cutaneous colonization model demonstrated *S. aureus* strain-specific differences in eliciting skin inflammation and immune signatures characteristic of AD patients. Specifically, *S. aureus* isolates from AD patients with more severe flares induced epidermal thickening and expansion of cutaneous T helper 2 (T_H2) and T_H17 cells. Integrating high-resolution sequencing, culturing, and animal models demonstrated how functional differences of staphylococcal strains may contribute to the complexity of AD disease.

Sci trasl Med 2017; 9: eaal4651

Eitan Israeli