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The Relationship between Syringoma and Common Metabolic and Endocrine Disorders: Retrospective Analysis

Siringoma ile Yaygın Metabolik ve Endokrin Bozukluklar Arasındaki İlişki: Retrospektif Analiz

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The research was conducted at Ankara Atatürk Training and Research Hospital, which has since been transformed into Ankara Bilkent City Hospital.

ABSTRACT Objective: Syringomas are benign tumors of eccrine sweat glands. Their multifactorial etiology involves hormonal, inflammatory, autoimmune, and genetic factors. The study aimed to assess the prevalence of common metabolic and endocrine disorders, including diabetes mellitus (DM), hyperlipidemia, and thyroid disorders, in syringoma patients. **Material and Methods:** This retrospective cross-sectional study analyzed data from 42 syringoma patients, including demographics, syringoma form (localized or generalized), and lesion locations. Biochemical, hormonal test results, thyroid autoantibody assays, and available skin biopsy reports were also reviewed. The presence of DM, hyperlipidemia, and thyroid disorders was assessed based on medical diagnosis records and laboratory findings. **Results:** The mean age of the patients was 38.5±12.8 years (range 19-66), with 78.6% female. Localized syringomas were found in 25 (59.5%) patients, mostly in the periorbital area, while generalized eruptive syringomas were seen in 17 (40.5%) patients, primarily affecting the trunk and chest. Thyroid disorders were present in 28.6%, hyperlipidemia in 23.8%, and DM in 11.9%. No significant differences were observed between localized and generalized syringomas regarding DM (p=0.14), hyperlipidemia (p=0.27), and thyroid disorders (p=0.73). Five (11.9%) patients had hypothyroidism, and 1 (2.4%) had hyperthyroidism. Elevated antithyroid antibodies were found in 8 (19%) patients, 6 euthyroid and 2 with hypothyroidism (Hashimoto's thyroiditis). **Conclusion:** This study identified a potential link between syringomas and thyroid disorders, while the prevalence of hyperlipidemia and DM was consistent with general population averages. However, comparisons with the general population were descriptive and not statistically tested, meaning the observed higher prevalence of thyroid disorders may suggest a potential association rather than a definitive link. The findings indicate a possible autoimmune component in syringoma pathogenesis. Further research with larger sample sizes and controlled studies is needed to confirm this relationship.

Keywords: Diabetes mellitus; endocrinopathies; hyperlipidemia; syringoma; thyroid dysfunction

ÖZET Amaç: Siringoma, ekrin ter bezlerinin benign tümörüdür. Hormonal, inflamatuar, otoimmün ve genetik faktörleri içeren multifaktöriyel bir etiyolojiye sahiptir. Bu çalışmada, siringoma hastalarında diabetes mellitus (DM), hiperlipidemi ve tiroid hastalıkları gibi yaygın metabolik ve endokrin bozuklukların prevalansının değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu retrospektif kesitsel çalışmada, 42 siringoma hastasının demografik özellikleri, siringoma formu (lokalize veya jeneralize) ve lezyon yerleşim yerleri analiz edilmiştir. Ayrıca biyokimyasal, hormonal test sonuçları, tiroid otoantikor testleri ve mevcut deri biyopsi raporları da incelenmiştir. DM, hiperlipidemi ve tiroid hastalıklarının varlığı, tıbbi tanı kayıtları ve laboratuvar bulguları doğrultusunda değerlendirilmiştir. **Bulgular:** Hastaların yaş ortalaması 38,5±12,8 (aralık 19-66) yıl olup, %78,6'sı kadın idi. Lokalize siringoma, 25 (%59,5) hastada ve çoğunlukla periorbital bölgede görülürken; jeneralize erüptif siringoma, 17 (%40,5) hastada ve genellikle gövde ve göğüs bölgesinde tespit edilmiştir. Tiroid hastalıkları %28,6, hiperlipidemi %23,8 ve DM %11,9 oranında gözlenmiştir. Lokalize ve jeneralize siringomalar arasında DM (p=0,14), hiperlipidemi (p=0,27) ve tiroid hastalıkları (p=0,73) açısından anlamlı fark saptanmamıştır. Beş (%11,9) hastada hipotiroidi, 1 (%2,4) hastada hipertiroidi mevcuttur. Sekiz (%19) hastada yüksek antitiroid antikor düzeyleri saptanmış olup, bunların 6'sında ötiroid, 2'sinde hipotiroidi (Hashimoto tiroiditi) izlenmiştir. **Sonuç:** Bu çalışma, siringomalar ile tiroid hastalıkları arasında potansiyel bir ilişki olduğunu ortaya koymuştur. Ayrıca hiperlipidemi ve DM prevalansı, genel popülasyon ortalamalarıyla uyumlu bulunmuştur. Ancak genel popülasyonla yapılan karşılaştırmalar tanımlayıcı nitelikte olup, istatistiksel olarak test edilmemiştir. Dolayısıyla tiroid hastalıklarının daha yüksek prevalansı kesin bir ilişkiyi değil, yalnızca olası bir bağlantıyı düşündürmektedir. Bulgular, syringoma patogenezinde olası bir otoimmün bileşene işaret etmektedir. Bu ilişkinin doğrulanması için daha büyük örneklem büyüklükleri ve kontrollü çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Diabetes mellitus; endokrinopatiler; hiperlipidemi; siringoma; tiroid disfonksiyonu

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Syringomas are common benign adnexal tumors of eccrine sweat glands, often presenting as asymptomatic, skin-colored or yellowish papules, typically measuring a few millimeters in diameter. These papules are frequently clustered around the eyelids but can also manifest on other areas such as the face, axillae, umbilicus, upper chest, and vulva. Syringomas predominantly occur in females and usually present during early adulthood.[1,2] Clinically, syringomas can be classified into 4 forms: localized, familial (autosomal dominant inheritance), generalized (including multiple and eruptive syringomas), and those associated with Down syndrome.[3]

The pathogenesis of syringomas remains largely unknown. It has been suggested that pluripotent stem cell hamartomas might underlie the development of eruptive syringomas. Another theory posits that they result from benign hyperplasia of intraepidermal eccrine ducts, possibly as a response to inflammatory stimuli rather than true neoplastic proliferation. Additionally, a potential hormonal influence could explain the female predominance of the condition.[4,5] Another hypothesis proposes that the hyperglycemia associated with diabetes mellitus (DM) causes glycogen to accumulate in both the skin and the clear cells of syringomas, a rare histological variant. Therefore, it is advisable to check for underlying DM in patients with clear cell syringomas.[1,6]

Beyond the clear cell variant, however, the relationship between syringomas and other endocrinopathies remains less defined. This study aimed to investigate the prevalence of common endocrinopathies, including DM, thyroid disorders, and hyperlipidemia, among syringoma patients.

MATERIAL AND METHODS

ETHICAL APPROVAL

The study adhered to the principles of the Helsinki Declaration. Approval for the study was obtained from the Clinical Research Ethics Committee of Ankara Atatürk Training and Research Hospital (date: June 10, 2015; no: 121).

STUDY DESIGN

This retrospective cross-sectional study was conducted using data from 42 patients with syringomas who visited the Ankara Atatürk Training and Research Hospital, Dermatology and Venereal Diseases outpatient clinic between January 2010-December 2018. Data were extracted from the hospital's automation system, including patient demographics (age and gender), duration and form of syringoma (localized or generalized), locations of lesions, as well as biochemical and hormonal tests, thyroid autoantibody assays, and skin biopsy pathology reports when available. All patients included in the study had been systematically screened for DM, hyperlipidemia and thyroid disorders. Patients with incomplete or unavailable records in the hospital database were excluded from the study. The study also excluded individuals under 18 years of age, pregnant patients and those with malignancies.

The presence of DM, hyperlipidemia, and thyroid disorders was assessed based on medical diagnosis records and laboratory findings. Patients with documented diagnoses or laboratory results meeting the following diagnostic criteria were classified as positive for the respective conditions.

- DM: Fasting plasma glucose ≥126 mg/dL, 2-hour post- oral glucose tolerance test glucose ≥200 mg/dL, or hemoglobin A1c ≥6.5%.
- Hyperlipidemia: Total cholesterol >200 mg/dL, low density lipoprotein >100 mg/dL, triglycerides >150 mg/dL, high density lipoprotein <60 mg/dL.
- Thyroid dysfunction: Thyroid-stimulating hormone levels outside the reference range of 0.27-4.2 mIU/L and free T4 outside the reference range of 0.93-1.71 ng/dL.
- Elevated antibodies: Anti-thyroglobulin antibody >115 IU/mL, anti-thyroid peroxidase antibody >34 IU/mL

Patients without a documented diagnosis of these conditions and whose relevant laboratory parameters fell within normal reference ranges were classified as not having the respective disorders.

42 patients were divided into 2 groups, localized and generalized syringoma, according to the Friedman and Butler classification.[3]

STATISTICAL ANALYSIS

The data obtained were analyzed using SPSS for Windows 26.0. Descriptive statistical methods, including number, percentage, mean, and standard deviation, were employed for data evaluation. The relationship between variables was assessed using Fisher's exact test. p value <0.05 was accepted statistically significant.

RESULTS

A total of 42 patients diagnosed with syringoma were included in the study. The demographic and clinical characteristics of the patients are summarized in Table 1. The mean age of the participants was 38.5±12.8 years, with a range from 19 to 66 years. The majority of patients were female (78.6%), and the mean duration of syringoma was 8.57±7.60 years, with a duration range of 1 to 30 years.

The detailed distribution of syringoma localizations in patients with localized and generalized eruptive syringoma is shown in Table 2. Localized syringoma was identified in 25 (59.5%) patients, with most lesions appearing in the periorbital area (23 patients). Meanwhile, 17 (40.5%) patients exhibited generalized eruptive syringoma, which had a broader distribution. The trunk was the most commonly affected area (8 patients), followed closely by the chest (7 patients).

The prevalence of endocrinopathies among the patients is presented in Table 3. The most common endocrinopathies observed were thyroid disorders, present in 28.6% of the patients, followed by hyperlipidemia (23.8%) and DM (11.9%). No statistically significant difference was found between the localized and eruptive syringoma patient groups in terms of the evaluated endocrinopathies (p>0.05).

Thyroid diseases included the following: 5 (11.9%) patients were diagnosed with hypothyroidism, 2 (4.8%) of whom had Hashimoto's thyroiditis, and 1 (2.4%) patient had hyperthyroidism. Thus, a total of 6 (14.3%) patients were found to have thyroid dysfunction. Additionally, 8 (19%) patients had elevated anti-thyroglobulin and/or anti-thyroid peroxidase antibody levels, of which 6 were euthyroid and 2 had hypothyroidism (Table 4).

In the histopathological examination of skin biopsies from 10 patients, the report described epithelial cell cords and nests within dense fibrous stroma in the dermis, along with tubules lined by 2 rows of epithelium, some showing comma or racket-shaped structures. One case of eruptive syringoma revealed cytoplasmic clearing of ductal cells, identified as the rare "clear cell variant". This patient did not have DM, but high thyroid autoantibodies were detected.

DISCUSSION

Syringomas are benign adnexal tumors with an unclear etiology, though hormonal factors, inflammation, and genetic predispositions have been

TABLE 1: Demographic and clinical characteristics of syringoma patients

Characteristics	All syringoma patients (n=42)
Mean age, years (±SD)	38.5±12.8
(minimum-maximum)	(19-66)
Gender	
Male (%)	9 (21.4)
Female (%)	33 (78.6)
Duration of syringoma	8.57±7.60
(minimum-maximum)	(1-30)

SD: Standard deviation

TABLE 2: Distribution of syringoma localizations in patients with localized and generalized eruptive syringoma

	Syringoma localizations						
Syringoma types	Periorbital	Face (nonperiorbital)	Neck	Chest	Arms	Trunk	Vulva
Localized syringoma n=25 (59.5%)	23	1	1	-	-	-	-
Generalized eruptive syringoma n=17 (40.5%)	6	2	6	7	5	8	1
Total n=42	29 (69%)	3 (7.1%)	7 (16.7%)	7 (16.7%)	5 (11.9%)	8 (19%)	1 (2.4%)

TABLE 3: Prevalence of metabolic and endocrine disorders in patients with localized and generalized eruptive syringoma

Endocrinopathy	Localized syringoma (n=25)	Generalized eruptive syringoma (n=17)	Total (n=42)	p value*
Diabetes mellitus	1 (4%)	4 (23.5%)	5 (11.9%)	0.14
Hyperlipidemia	4 (16%)	6 (35.3%)	10 (23.8%)	0.27
Thyroid disorders	8 (32%)	4 (23.5%)	12 (28.6%)	0.73

*Fisher's exact test; A p value of <0.05 was considered statistically significant.

TABLE 4: Distribution of thyroid disorders

Thyroid disorders (n=12)	n	%
Thyroid dysfunction (hypo+hyper)	6	14.3
-Hypothyroidism	5	11.9
Hashimoto's thyroiditis*	2	4.8
-Hyperthyroidism	1	2.4
Elevated anti-Tg and/or anti-TPO antibodies	8	19
-Euthyroid with elevated antibodies	6	14.3
-Hypothyroidism with elevated antibodies*	2	4.8

*Represent the same group of patients; Tg: Thyroglobulin; TPO: Thyroid peroxidase

implicated. Associations with DM and autoimmune conditions suggest a potential link to metabolic and immunological pathways.[1] Given these uncertainties, we conducted this study to further investigate the pathogenesis of syringomas and their potential comorbidities.

Our study found that 78.6% of syringoma patients were female, which aligns with the existing literature, where syringomas are reported to occur in females between 55% and 97%. This confirms the strong female predominance of the condition. Syringomas usually appear during puberty or in the third to fourth decades of life, and in our patient group, the mean age of 38.5 years aligns with the previously reported onset age range.[7]

Regarding localization, syringomas most commonly occur in the periorbital area.[1] Our findings are in agreement with this, as the majority of our patients had periorbital involvement. Eruptive syringomas, however, tend to affect regions such as the anterior chest, abdomen, axillary, and periumbilical areas. Consistent with this, in our study, the trunk was the most frequently affected site, followed closely by the chest.[8] The literature states that although syringoma is relatively common, the eruptive variant remains rare.[9] In a study involving 244 syringoma patients, 29.2% presented with the eruptive form.[7] Interestingly, in our study, the rate of eruptive syringoma was higher at 40.5%. This discrepancy may be attributed to regional or genetic factors, and it is also possible that patients with localized forms of syringoma may not seek medical attention. However, these potential explanations are hypothetical.

Syringomas have a multifactorial etiology, with key influences including hormonal, inflammatory, autoimmune, and genetic factors.[10] The prevalence of these lesions in post-pubertal females and during pregnancy, along with the overexpression of estrogen and progesterone receptors, highlights the role of hormones.[11-13] Inflammation has also been implicated, with cases linked to irritation or pre-existing conditions like eczema, supported by lymphocytic infiltrates around eccrine ducts and superficial blood vessels.[4,14] Some patients also present with autoimmune conditions like alopecia areata and vitiligo.[15,16] Immunohistochemical analysis of syringoma tissue has revealed that the autoimmune inflammatory infiltrates around the sweat ducts contain a balanced mix of CD4+ and CD8+ T cells, indicating that reactive hyperplasia of eccrine ducts may result from autoimmune damage to their surface components.[17] Additionally, syringomas can sometimes be associated with hereditary or systemic diseases, including hyperthyroidism, DM, Marfan syndrome, and Ehlers-Danlos syndrome.[10]

In terms of the association between syringomas and thyroid disorders, Aliagaoglu et al. were the first to report a case in the literature of a woman with hyperthyroidism and unilateral syringomas on her face.[18] Polat et al. later published a second case of eruptive syringomas in a patient with hyperthyroidism.[19] Most recently, in 2016, a third case involving a male patient with eruptive syringomas and hyperthyroidism was reported.[20]

The prevalence of Hashimoto's thyroiditis in the general population is estimated at 2%.[21] In healthy population, the prevalence of anti-thyroglobulin antibodies is reported at 11.5%, while anti-thyroid peroxidase antibodies are observed in 13% of cases.[22] Additionally, in Türkiye, the prevalence of clinical hyperthyroidism and hypothyroidism in the general population has been found to be 0.5% and 1.4%, respectively.[23] As with other autoimmune diseases, Hashimoto's thyroiditis is more common in women, attributed to the stronger cellular and humoral immune response in females. Immune cells express estrogen, progesterone, and testosterone receptors. High estrogen levels are linked to increased inflammation and autoantibody production, whereas high progesterone levels exert anti-inflammatory effects.[24-27] To our knowledge, our study is the first to explore the potential link between syringomas and thyroid pathologies. Based on the findings of our study, the prevalence of both hypothyroidism and hyperthyroidism in patients with syringomas is higher than in the general population. Interestingly, although syringomas are typically associated with hyperthyroidism in the literature, our results show a notable occurrence of hypothyroidism as well.

From an autoimmune perspective, our study revealed an increased frequency of thyroid antibodies and Hashimoto's thyroiditis in patients with syringomas compared to the general population. This may suggest a possible autoimmune component in the pathogenesis of syringomas.

Although our study suggests a potential link between thyroid disorders and syringomas, it is important to recognize that the small sample size and lack of a control group limit the ability to draw definitive conclusions. The findings indicate a higher prevalence of thyroid dysfunctions, including both hypothyroidism and hyperthyroidism, in syringoma patients compared to the general population, but this does not imply a direct causality. Given the retrospective nature of the study and the absence of statistical comparison with a control group, further prospective studies with larger sample sizes and controlled designs are necessary to confirm whether thyroid disorders are indeed related to the pathogenesis of syringomas or if these findings are coincidental.

Independent of syringomas, a relationship between thyroid disorders and breast cancer has also been established, attributed to the activation of estrogen receptors in breast cells by thyroid hormones.[28] In light of this, our findings, along with cases in the literature, suggest that the coexistence of syringomas and thyroid disorders may also be related to estrogen hormone activity or estrogen receptors. However, this potential link requires further investigation and should currently be considered speculative.

Clear cell syringomas are a rare histological variant of syringomas, characterized by ductal epithelial cells with a bright, clear cytoplasm due to an increased amount of intracellular glycogen. Clinically, clear cell syringomas appear similar to regular syringomas and are considered a potential cutaneous indicator of DM.[9,29] In our study, however, the patient with clear cell syringoma did not have DM, but thyroid auto-antibodies were detected. It is important to note that this is a single case, and generalizations should not be made. On the other hand, DM was observed in 5 (11.9%) of our cases. Recent studies have shown that the prevalence of DM in the Turkish population is 13.7% according to national data.[23,30] The proportion of patients with DM in our study was consistent with this figure.

In Türkiye, approximately one in three adults has hypercholesterolemia, and one in three has elevated triglyceride levels.[31] In our study, hyperlipidemia was identified in 23.8% of syringoma patients. This suggests that the presence of syringomas does not appear to be linked with an increased risk of hyperlipidemia.

Our analysis revealed that while approximately one-quarter of patients with generalized eruptive syringoma had DM (23.5%) and one-third had hyperlipidemia (35.3%), these conditions did not show a statistically significant predominance over localized forms. Thyroid disorders were observed in around one-third (32%) of patients with localized syringomas and one-quarter (23.5%) of those with generalized eruptive syringomas. Although the distribution of comorbidities appeared similar between localized and generalized forms, the small sample size may have limited the ability to detect significant differ-

ences. Future studies with larger cohorts are needed to better evaluate these relationships and to draw more generalizable conclusions.

This study has several limitations, including its single-center retrospective design, small sample size, and focus solely on the Turkish population, which may limit the generalizability of the findings. Importantly, the absence of a matched control group without syringoma limits the strength of the conclusions. In this study, comparisons with the general population were descriptive in nature and not supported by statistical testing; therefore, the observed higher prevalence of thyroid disorders and similar rates of DM or hyperlipidemia in patients with syringoma may only suggest a potential association rather than confirm a definitive link. Further research with larger sample sizes, appropriate control groups, and statistical comparisons is needed to determine whether these comorbidities are coincidental or linked to the pathogenesis of syringomas. Additionally, investigating the prevalence of syringomas in patients with pre-existing metabolic disorders could also offer statistically more robust insights and represents a potential avenue for future research.

CONCLUSION

The aim of this study was to highlight the metabolic and endocrine disorders associated with syringomas. A potential link between syringomas and thyroid pathologies was identified; however, the prevalence of hyperlipidemia and DM remained consistent with general population averages. The observed increased frequency of thyroid disorders suggests a possible autoimmune component in the pathogenesis of syringomas. In light of these findings, evaluation of thyroid function and autoantibodies in syringoma patients may be considered, and larger, controlled studies are needed to confirm this potential relationship.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sertaç Şener;* ***Design:*** *Sertaç Şener;* ***Control/Supervision:*** *Sertaç Şener, Cansu Altınöz Güney, Ahmet Metin;* ***Data Collection and/or Processing:*** *Sertaç Şener, Fadime Kılınç, Ayşe Akbaş, Huban Sibel Orhun, Ahmet Metin, Saliha Kırbaş;* ***Analysis and/or Interpretation:*** *Cansu Altınöz Güney;* ***Literature Review:*** *Cansu Altınöz Güney, Sertaç Şener, Fadime Kılınç;* ***Writing the Article:*** *Cansu Altınöz Güney;* ***Critical Review:*** *Cansu Altınöz Güney, Sertaç Şener, Fadime Kılınç, Ayşe Akbaş, Huban Sibel Orhun, Ahmet Metin, Saliha Kırbaş;* ***References and Fundings:*** *Sertaç Şener;* ***Materials:*** *Sertaç Şener, Huban Sibel Orhun.*

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