DERMATO-ENDOCRINOLOGY
2018, VOL. 9, NO. 1, e1405198 (4 pages)
https://doi.org/10.1080/19381980.2017.1405198

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RESEARCH PAPER/REPORT

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Thyroid autoimmunity in female post-adolescent acne: A case-control study

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Introduction

Acne vulgaris is an incompletely understood disorder of poliosebaceous follicles. A scourge of adolescence, it is increasingly persisting into the mid-forties, especially in females. 45% of women aged 21–30 years, 26% aged 31–40 years, and 12% aged 41–50 years, suffer from clinically-visible acne.[1] The reasons for this rising prevalence have been unclear. Polycystic ovarian syndrome (PCOS) has been suggested as a possible contributor, however most acne sufferers have normal serum androgen levels.[2,3]

There has been increasing suspicion of a key autoinflammatory role in pathogenesis of chronic acne vulgaris. Autoinflammatory syndromes associated with acne have been described as possibly sharing common pathogeneses, involving dysregulated immunity with abnormal interleukin-1 signaling, leading to clinically significant inflammation.[4,5] Thyroid autoimmunity has been detected in a number of chronic inflammatory skin conditions including acne vulgaris and chronic idiopathic urticaria.[6,7]

In 2012, Vergou and colleagues were the first to show female post-adolescent acne sufferers had significantly higher rates of thyroid autoimmunity compared with healthy controls.[7] The relationship has not been examined since, despite a sound theoretical grounding. We aimed to confirm this association between thyroid autoimmunity and post-adolescent acne in adult women, as well as qualify its practical value with subsequent endocrinologist referral and intervention.

Results

130 patients and 65 controls satisfied the inclusion criteria and were enrolled in the study. Patients and controls had consulted one of 10 different family physicians. Patients ages ranged from 21 to 36 years with a median age of 26 years. Controls ages ranged from 20 to 37 with a median age of 27 years.

116/130 (89%) patients and 60/65 (92%) controls returned thyroid function tests in the normal range (TSH 0.4–5.0mIU/L, FT4 10–20pmol/L, FT3 2.3–5.7pmol/L. The most prevalent abnormal thyroid function finding was a high TSH in the setting of a normal FT3 and FT4 (See Table 1).

32/130 (24.5%) patients recorded positive (>20IU/ml) anti-thyroglobulin antibodies compared with 7/65 (10%) controls. 24/130 (18%) patients recorded positive (>35IU/ml) anti-TPO antibodies compared with 4/65 (6%) controls. 7/130 (5%) patients recorded both positive anti-thyroglobulin and anti-TPO antibodies compared with 0/65 (0%) controls.

There was a statistically significant difference between the groups for positive anti-TG ($p = 0.023$) and anti-TPO ($p = 0.021$) antibodies but not for presence of both ($p = 0.098$) (Table 2). Differences in TSH, FT3 and FT4 between the groups were not statistically significant. There was no statistically significant association between abnormal thyroid function tests and positive thyroid antibodies.

Patient follow-up after referral

95 patients were referred to one of eight endocrinologists and 89 successfully made contact with the spe-

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Table 1. Results of serum thyroid function testing (TSH, FT4, FT3).

	Patients (n = 130)	Controls (n = 65)
All normal	116	60
High TSH alone	8	2
Low TSH alone	1	1
High TSH, Low FT4	2	2
Low TSH, High FT4	2	0
High TSH, Low FT3	1	0
Low TSH, High FT3	0	0

Table 3. Outcomes of endocrinological referral.

Endocrinological intervention	n = 35
Active surveillance	9
Selenium	8
Thyroxine	16
Antithyroid medication (carbimazole or propylthiouracil)	3
Radioiodine treatment	2
Surgery	3

cialist, for which we were able to source return correspondence for 82.

35/82 (42%) patients indicated some form of thyroid intervention which consisted of at least one of the following: active surveillance, selenium, thyroxine, antithyroid medication, radioiodine treatment or surgery (Table 3).

Discussion

Acne pathogenesis involves an interplay of follicular hyperkeratinisation, sebum production, Cutibacterium acnes (C. acnes) and inflammation. It is less clear in adult acne but smoking, genetics, resistant bacteria, oral contraceptives, cosmetics and underlying hormone abnormalities have all been implicated.[8] McGeown et al. [9] found higher sebum excretion rates in women with post-adolescent acne compared with non-acne sufferers, and PCOS is the leading theory, however the majority of patients with adult acne have normal androgen levels.

Thyroid hormone action on sebaceous glands is unclear. In hypothyroid states, sebocytes exhibit reduced rates of secretion (SER),[10] and TSH and Thyroxine, with co-administration of testosterone, have both been shown to increase sebum secretion.[11] Although SER increases with thyroxine, it still remains subnormal.[12] Studies have failed to show significant changes in thyroid function parameters in adult acne.[7,13] The exact role of thyroid hormone remains unclear but it seems unlikely that it is mediated principally through sebum secretion.

Table 2. Differences in thyroid function and antibody testing between groups.

	Patients	Controls	P-value	Odds ratio (95% CI)
Anti-TG	32	7	0.023	2.7
Anti-TPO	24	2	0.021	3.45
Both	7	0	0.098	n/a

Susceptibility to autoimmune thyroid diseases (AITD) depends on a complex interaction between environmental and genetic factors. 79% of autoimmune thyroid disease may be attributed to genetics.[14] Cytokines are crucial in the regulation of immune and inflammatory responses and are the probable candidate genes for autoimmune thyroid disease. Immunomodulatory genes coding for pro-inflammatory cytokines such as interleukin-1 and interferon-γ have thus far been implicated in pathogenesis.[15]

In autoimmunity, thyroid follicular cells are induced to express Fas ligand by cytokine stimulation and antigen-presenting and Th1 cells (e.g. interleukin-1), leading to apoptosis. IN Hashimoto's disease, apoptosis occurs in thyroid cells expressing Fas, or normal thyroid cells in which Fas was induced by IL-1ß. So, any event in a primed individual may lead to local production of IL-1ß initiating thyroid-cell induced apoptosis. TG and TPO antibodies develop secondarily to this thyroid damage inflicted by T lymphocytes.[16,17]

There is a more than four-fold risk of acne vulgaris in individuals with affected first-degree family members.[18] As well as in autoimmune thyroid disease, IL-1ß may also play an important role in the development of inflammation in acne. IL-1ß has been shown to propagate inflammation initiated by C. acnes in human sebocytes.[19,20] We suspect this complex interaction between genetics, thyroid and sebaceous glandular tissue may help produce the inflammatory changes of post-adolescent acne observed in thyroid autoimmune states.

Our results suggest thyroid antibody testing is indeed warranted in female adult acne as subsequent referral of positive results leads to intervention in a high proportion (42.5%) of patients. Prophylaxis for euthyroid autoimmune thyroiditis remains controversial but has shown benefit.[21,22] Additionally, as TG and TPO antibodies are often positive in other autoimmune conditions, prudent testing in this cohort

may also alert the clinician to screen for important comorbidities including diabetes mellitus and systemic lupus erythematosus.[23,24]

The study was limited by its retrospectivity and small sample size. Inclusion of consults from 10 family physicians and 8 endocrinologists may have introduced some heterogeneity in our assessments. Another criticism may be that acne vulgaris diagnoses were not confirmed by a skin specialist, however research has shown that diagnostic agreement between family practitioners and dermatologists for acne is very high.[25] likely due in no small part to its significant presence in primary care.

Based on our findings we suggest thyroid autoantibody testing should be routine in women with post-adolescent acne, as positive results may signify a joint presentation qualifying endocrinological input. Even minor derangements should meet a low threshold for referral and importantly, antibody testing retains its value in the setting of a normal screening TSH. Future work should confirm this association in larger cohorts and explore the possible shared genetics between these two conditions.

Patients and methods

We retrospectively screened the electronic records from 2010–2016 at a private family medicine clinic in Sydney for women who had consulted one of the clinic doctors for post-adolescent acne (persisting >21 years of age). Included patients had only been given a categorical diagnosis of acne vulgaris and severity of acne was not quantified.

Subjects were required to have had thyroid-stimulating hormone (TSH), free T3 (FT3), free T4 (FT4), anti-thyroglobulin (anti-TG) and anti-tissue peroxidase (anti-TPO) antibody testing within 12 months of their acne presentation. Thyroid function results were categorised as high, normal or low and antibody tests as either positive or negative.

Subjects with known thyroid disease, PCOS or taking oral contraceptives or antiandrogens were excluded. Records were adjunctively screened for referral to, and correspondence from an endocrinologist.

We randomly selected age- (+/− 12 months) and sex-matched healthy controls from the same population who had presented for reasons not related to acne or any hormonal conditions with skin manifestations. Controls were required to have had the same thyroid function and antibody testing as patients during the study period. Controls with known thyroid disease or taking oral contraceptives or antiandrogens were excluded.

Ethics approval was not sought for this study as all data had been collected as part of the patients routine care at a private institution and is owned in its entirety by the second author. Study procedures were carried out in accordance with the Helsinki Declaration of 1975.

Statistics

Pearson Chi-square and Fisher's exact test were used to compare categorical variables. Stata's tables for epidemiologists was used to calculate odds ratios. A p-value of <0.05 was considered significant. Analysis was carried out using STATA14 software.

References

1. Perkins AC, Maglione J, Hillebrand GG, Miyamoto K, Kimball AB. Acne vulgaris in women: prevalence across the life span. J Womens Health. 2012;21:223–230.
2. Zouboulis CC. Acne vulgaris. The role of hormones. Hautarzt. 2010;61(2):107–8.
3. Cibula D, Hill M, Vohradnikova O, Kuzel D, Fanta M, Zivny J. The role of androgens in determining acne severity in adult women. Br J Dermatol. 2000;143:399–404.
4. Faleri S, Feichtner K, Ruzicka T. Severe acne in autoinflammatory diseases. Hautarzt. 2016;67(11):897–901.
5. Vinkel C, Thomsen SF. Autoinflammatory syndromes associated with hidradenitis suppurativa and/or acne. Int J Dermatol. 2017;56(8):811–818.
6. Nuzzo V, Tacuhmanova L, Colasanti P, Zuccoli A, Colao A. Idiopathic chronic urticaria and thyroid autoimmunity: Experience of a single center. Dermatoendocrinol. 2011;3(4):255–258.
7. Vergou T, Mantzou E, Tseke P, Moustou AE, Katsambas A, Alevizaki M, Antoniou C. Association of thyroid autoimmunity with acne in adult women. J Eur Acad Derm Venereol. 2012;26:413–416.
8. Knaggs HE, Wood EJ, Rizer RL, Mills OH. Post-adolescent acne. Int J Cosmet Sci. 2004;26:129–138.
9. McGeown CH, Goulden V, Holland DB, Ingham E, Cunliffe WJ. Sebum excretion rate in post-adolescent acne compared to controls and adolescent acne. J Invest Dermatol. 1997;108:386.
10. Shuster S, Thody AJ. The control and measurement of sebum secretion. J Invest Dermatol. 1974;62(3):172–190.
11. Ebling FJ, Ebling E, Skinner J. The effects of thyrotrophic hormone and of thyroxine on the response of the

sebaceous glands of the rate to testosterone. J Endocrinol. 1970;48(1):83–90.
12. Goolamali SK, Evered D, Shuster S. Thyroid disease and sebaceous function. Br Med J. 1976;1(6007):432–433.
13. Ekiz O, Balta I, Unlu E, Bulbul Sen B, Rifaioglu EN, Dogramaci AC. Assessment of thyroid function and lipid profile in patients with post-adolescent acne in a mediterranean population from Turkeyg. Int J Dermatol. 2015;54(12):1376–81.
14. Sgarbu JA, Maciel RM. Pathogenesis of autoimmune thyroid diseases. Arq Bras Endocrinol Metabol. 2009;53(1):5–14.
15. Hunt PJ, Marshall SE, Weetman AP, Bell JI, Wass JA, Welsh KI. Cytokine gene polymorphisms in autoimmune thyroid disease. J Clin Endocrinol Metab. 2000;85(5):1984–8.
16. Lacka K, Paradowska-Gorycka A, Maciejewski A. Interleukin 1 beta gene polymorphisms (SNP-511 and SNP+3953) in Hashimoto's thyroiditis among the polish population. Exp Clin Endocrinol Diabetes. 2014;122(9):544–7.
17. Wong KH, Rong SS, Chong KKL, Young Al, Pang CP, Chen LJ. Genetic associations of interleukin-related genes with graves' ophthalmopathy: A systematic review and meta-analysis. Sci Rep. 2015;5:16672.
18. Goulden V, McGeown CH, Cunliffe WJ. The familial risk of adult acne: a comparison between first-degree relatives and unaffected individuals. B J Dermatol. 1999;141 (2):297–300.
19. Kistowska M, Gehrke S, Jankovic D, Kerl K, Fettelschoss A, Feldmeyer L, Fenini G, Kolios A, Navarini A, Ganceviciene R, et al. IL-1beta drives inflammatory responses to Propionibacterium acnes in vitro and vivo. J Invest Dermatol. 2014;134(3):677–85.
20. Li ZJ, Choi DK, Sohn KC. Propionibacterium acne activates the NLRP3 inflammasome in human sebocytes. J Invest Dermatol. 2014;134(11):2747. Epub2014 May 12.
21. Gartner R, Gasnier BCH, Dietrich JW, Krebs B, Angstwurm MW. Selenium supplementation in patients with autoimmune thyroiditis decreases thyroid peroxidase antibodies concentrations. J Clin Endocrinol Metab. 2002;87 (4):1687–1691.
22. Aksoy DY, Kerimoglu U, Okhur H, Canpinar H, Karaagaoglu E, Yetgin S, Kansu E, Gedik O. Effects of prophylactic thyroid hormone replacement in euthyroid Hashimoto's thyroiditis. Endocr J. 2005;52(3):337–43.
23. Chang CC, Huang CN, Chuan LM. Autoantibodies to thyroid peroxidase in patients with type 1 diabetes in Taiwan. Eur J Endocrinol. 1998;139:44–48.
24. Pyne D, Isenberg D. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis. 2002;61 (1):70–72.
25. Castillo-Arenas E, Garrido V, Serrano-Ortega S. Skin conditions in primary care: An analysis of referral demand. Acta Dermosifiliogr. 2014;105:271–5.