Report

Acne keloidalis nuchae and thyroid diseases: a population-based cohort study

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Abstract

Background The association between acne keloidalis nuchae (AKN) and thyroid diseases is yet to be investigated.

Objective To evaluate the risk of developing hypothyroidism and hyperthyroidism among patients with AKN and to characterize the patients who have AKN and thyroid comorbidities.

Methods A population-based cohort study was conducted comparing AKN patients (n = 2,677) with age-, gender-, and ethnicity-matched control subjects (n = 13,190) with regard to incident cases of hypothyroidism and hyperthyroidism. Adjusted hazard ratios (HRs) were estimated by Cox regression analysis.

Results The incidence rates of hypothyroidism among patients with AKN and controls were estimated at 2.15 (95% CI, 1.49-2.99) and 0.82 (95% CI, 0.66-1.00) cases/1000 person-years, respectively. The crude risk of developing incident hypothyroidism was 1.85-fold greater in patients with AKN (HR, 1.85; 95% CI, 1.24-2.78; \( P = 0.003 \)). The elevated risk persisted following the adjustment for putative confounders (adjusted HR, 1.72; 95% CI, 1.03-2.89; \( P = 0.040 \)). The risk of hyperthyroidism was comparable in patients with AKN and controls both in the crude (HR, 1.55; 95% CI, 0.57-4.22) and adjusted (adjusted HR, 1.92; 95% CI, 0.59-6.21) analyses. Patients with coexistent AKN and thyroid diseases were significantly older at the onset of AKN, had more prominent female preponderance, and had a higher burden of comorbidity.

Conclusions Patients with AKN are at an increased risk of hypothyroidism. Screening for hypothyroidism should be considered in AKN patients with a compatible clinical picture.

Introduction

Acne keloidalis nuchae (AKN) is a chronic inflammatory skin disease mainly affecting young adult men of African descent.1 AKN typically presents with small, smooth, firm papules admixed with occasional pustules on the occipital scalp and posterior neck (Figure 1A). Subsequently, papules resolve and leave small zones of alopecia within a field of keloid-like papules (Figure 1B).1 While the etiology of AKN is not well established, it is known to be triggered by chronic inflammation or occlusion of follicles due to haircutting practices, trauma, and friction.2,3 Additionally, systemic factors such as increased sensitivity or excess of androgens, infections, autoimmunity, and insulin resistance may also contribute to the development of AKN.4

Thyroid diseases can fall into one of several categories. Hypothyroidism disorders are characterized by lower production of thyroid hormones and commonly result in fatigue, weight gain, slow heart rate, dry skin, and constipation.5 Hyperthyroidism disorders, on the other hand, involve an overproduction of thyroid hormones that leads to irritability, anxiety, weight loss, fast heartbeat, diarrhea, and enlargement of the gland. Structural abnormalities of the gland (e.g., goiters) and thyroid tumors can produce the aforementioned symptoms as well.6

Recent literature displayed an association between thyroid disorders and follicular-related diseases, such as acne and
hidradenitis suppurativa. While there is no well-established mechanism that connects these conditions, several possible overlapping themes were postulated, including metabolic dysfunction, metformin effects, or other autoinflammatory mechanisms. However, this association has not been investigated in patients with AKN.

The aim of the current study was to evaluate the risk of thyroid diseases among patients with AKN relative to control subjects. We additionally aimed to assess whether patients with AKN and thyroid comorbid diseases differ from remaining patients with AKN.

Methods

Study design and setting

A retrospective, population-based, cohort study was conducted utilizing data from the Clalit Health Services (CHS) database. The current study followed patients with AKN longitudinally to assess whether they have an increased risk of having thyroid dysfunction in comparison to matched control subjects.

CHS is the largest health maintenance organization in Israel, ensuring a population of approximately 4,927,000 enrollees as of October 2018. CHS takes advantage of a comprehensive computerized database that is based on real-time input from clinical, pharmaceutical, and administrative operating systems. Data from hospitals, primary care physicians, and specialists reports were proven as a reliable source for a multitude of observational studies. The present study was held in accordance with the Declaration of Helsinki and was approved by the institutional ethical board of Ben-Gurion University and CHS.

Study population, outcome measures, and covariates

All medical files of CHS members were screened for the diagnosis of AKN, and data on all incident cases of AKN between 2005 and 2018 were retrieved. A comparison group of individuals without AKN was chosen through 1:5 matching based on age, gender, and ethnicity. The control group was randomly selected from the list of CHS members and was individually matched to cases. The age matching was grounded on the exact year of birth (1-year strata).

The diagnosis of AKN was based on the documentation of an AKN-specific diagnostic code registered by a CHS board-certified dermatologist, whether in community services, inpatient clinics, outpatient clinics, or during hospitalizations in dermatologic wards. The diagnosis of hypothyroidism and hyperthyroidism was retrieved from the chronic register of CHS. That is, the diagnosis of thyroid disturbances relies on documentation by a board-certified endocrinologist based on a compatible clinical picture and laboratory analyses. It is then manually validated by the managing general practitioner.

Outcome measures were adjusted for comorbidities as evaluated by Charlson comorbidity score, an epidemiological estimate of the extent, and severity of comorbidities of eligible patients. Since AKN is well-known for an ethnic predilection in Afro-American individuals, outcome measures were adjusted for African origin, which had been defined according to the country of origin. Smoking status was categorized as a current smoker or never/past smoker.

Statistical analysis

The distribution of sociodemographic and clinical factors was compared between patients with and without AKN using t-test and Chi-square test for continuous and categorical variables, respectively. Incidence rates of thyroid diseases were calculated for both AKN patients and controls and expressed as the number of events per 1,000 person-years. Hazard ratios (HRs) for the risk of incident hypothyroidism and hyperthyroidism were acquired by the use of Cox regression models. In order to fulfill the structure of a cohort study in which outcome follows exposure, the incidence of thyroid diseases during follow-up was calculated only for individuals without a history of these disorders before study initiation. To compare

Figure 1 (A) Follicular pustules and crusted papules on the posterior neck and occipital scalp of a 19-year-old male with early AKN; (B) Keloidal papulonodules associated with scarring alopecia on the occipital scalp of a 23-year-old male with late AKN

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The study population included 2,677 patients with AKN and 13,190 age-, gender-, and ethnicity-matched control subjects. The mean age of the study population was 34.5 ± 12.9, 95.7% of the study participants were men, and 60.8% were of Jewish ancestry. Comorbidity rates, measured by the Charlson comorbidity index, were greater among patients with AKN, with 138 (5.1%) AKN patients and 516 (3.9%) control subjects having severe comorbidity. The frequency of smoking was significantly higher among controls, whereas the mean BMI was significantly higher among patients with AKN (Table 1).

### Results

The incidence rates of hyperthyroidism among patients with AKN

The incidence rates of hyperthyroidism among patients with AKN and controls were estimated at 2.15 (95% CI, 1.49-2.99) and 0.82 (95% CI, 0.66-1.00) cases/1000 PY, respectively. The crude risk of developing incident hyperthyroidism was 1.85-fold higher among patients with AKN (HR, 1.85; 95% CI, 1.24-2.78; P = 0.003). In stratified analysis, the risk of new-onset hyperthyroidism was significantly increased among men (HR, 1.78; 95% CI, 1.24-2.80; P = 0.014) and younger individuals (<32.2 years-specific risk* 2.41 (1.24-4.67) 0.009). After controlling for the aforementioned variables and additionally to comorbidities (model 2), the risk fell shortly out of significance (adjusted HR, 1.60 (0.95-2.68); P = 0.076).

### Table 1 Descriptive characteristics of the study population

| Characteristic | Patients with AKN (n = 2,677) | Controls (n = 13,190) | P value |
|---------------|-------------------------------|-----------------------|---------|
| Age, years    |                               |                       |         |
| Mean ± SD     | 34.5 ± 12.9                   | 34.5 ± 12.9           | NS      |
| Median (range)| 32.2 (6.3-90.3)               | 32.1 (13.0-99.0)      |         |
| Male gender, n (%) | 2,562 (95.7%)               | 12,618 (95.7%)        | NS      |
| Ethnicity, n (%) |                             |                       |         |
| Jews          | 1,623 (60.6%)                 | 8,013 (60.8%)         | NS      |
| Arabs         | 1,054 (39.4%)                 | 5,177 (39.2%)         |         |
| Origin (Africans vs. Non-Africans), n (%) |                     |                       |         |
| Non-Africans  | 2,527 (94.4%)                 | 12,827 (97.2%)        | <0.001  |
| Africans      | 150 (5.6%)                    | 363 (2.8%)            |         |
| Charlson comorbidity score, n (%) |                   |                       |         |
| None (0)      | 1,889 (70.6%)                 | 10,366 (78.6%)        | <0.001  |
| Moderate (1-2)| 650 (24.3%)                  | 2,308 (17.5%)         | <0.001  |
| Severe (≥3)   | 138 (5.1%)                    | 516 (3.9%)            | 0.004   |
| Body mass index (Kg/m²), mean ± SD | 29.1 ± 6.7                  | 26.0 ± 6.9            | <0.001  |
| Smoking, n (%) | 1,038 (38.8%)                | 6,338 (48.1%)         | <0.001  |

### Abbreviations: AKN, acne keloidalis nuchae; N, number; SD, standard deviation.

The epidemiological features of AKN patients with and without thyroid conditions, all patients with both conditions were included in this cross-sectional comparison, even those who had their thyroid disease prior to the diagnosis of AKN. Two-tailed P-values less than 0.05 were considered statistically significant, whereas results with 95% confidence intervals (CIs) were reported where applicable. All statistical analyses were performed using SPSS software, version 25 (SPSS, Armonk, NY: IBM Corp.).

### Abbreviations: AKN, acne keloidalis nuchae; CI, confidence interval; HR, hazard ratio; PY, person-year.

**Bold:** significant value.

*Following the adjustment for age, gender, ethnicity (Jews vs. Arabs), and origin (African vs. non-Africans).

The risk of hypothyroidism among patients with AKN

The incidence rates of hypothyroidism among patients with AKN and controls were estimated at 0.33 (95% CI, 0.12-0.73) and 0.21 (95% CI, 0.13-0.34) cases/1000 PY, respectively. The crude risk of developing incident hypothyroidism was 1.85-fold higher among patients with AKN (HR, 1.85; 95% CI, 1.24-2.78; P = 0.003). In stratified analysis, the risk of new-onset hypothyroidism was significantly increased among men (HR, 1.78; 95% CI, 1.24-2.80; P = 0.014) and younger individuals (<32.2 years-specific risk* 2.41 (1.24-4.67) 0.009). After controlling for the aforementioned variables and additionally to comorbidities (model 2), the risk fell shortly out of significance (adjusted HR, 1.60 (0.95-2.68); P = 0.076).

We then assessed whether AKN imposes an independent risk of developing hypothyroidism by adjusting for multiple confounding factors. After controlling for demographic variables (model 1), AKN emerged as an independent risk factor of hypothyroidism (adjusted HR, 1.72; 95% CI, 1.03-2.89; P = 0.040). After controlling for the aforementioned variables and additionally to comorbidities (model 2), the risk fell shortly out of significance (adjusted HR, 1.64; 95% CI, 0.98-2.75; P = 0.061; Table 3).
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Table 3 Incidence rates and hazard ratio of new-onset hyperthyroidism among patients with AKN

| Patients with AKN | Controls |
|-------------------|----------|
| Median follow-up time, years | 5.8 (0.1-12.9) | 5.9 (0.0-13.7) |
| Number of events | 5 | 16 |
| Incidence rate/1000 PY | 0.33 | 0.21 |
| HR (95% CI) | 0.12-0.73 | 0.13-0.34 |

Unadjusted analysis
- Overall unadjusted risk: 1.55 (0.57-4.22)
- Male-specific risk: 1.06 (0.30-3.69)
- Female-specific risk: 5.03 (0.71-35.70)
- <32.2 years-specific risk: 0.83 (0.10-6.89)
- ≥32.2 years-specific risk: 1.96 (0.62-6.28)

Adjusted analysis
- Model 1*: 1.92 (0.59-6.21)
- Model 2*: 1.77 (0.55-5.71)

Abbreviations: AKN, acne keloidalis nuchae; PY, person-year; CI, confidence interval; HR, hazard ratio.

Bold: significant value.

*Following the adjustment for age, gender, ethnicity (Jews vs. Arabs), and origin (African vs. non-Africans).

The features of patients with AKN and thyroid disease

We then addressed the difference between patients with AKN and thyroid disorders (whether hyperthyroidism or hypothyroidism; n = 78), as compared to the remaining patients with AKN (n = 2,599). Patients in the former group presented with AKN at an older age, had higher female, Jewish, and non-African preponderance, higher average body mass index, and Charlson comorbidity score (Table 4).

Table 4 The clinical and demographic characteristics of patients with AKN and thyroid diseases as compared to the remaining patients with AKN

| AKN with thyroid disease (n = 78) | AKN without thyroid disease (n = 2,599) | P value |
|----------------------------------|----------------------------------------|---------|
| Age at the onset of AKN, mean (SD) | 40.9 (13.9) | 34.3 (12.8) | <0.001 |
| Female sex, n (%) | 12 (15.4%) | 103 (4.0%) | <0.001 |
| Jewish ethnicity, n (%) | 56 (71.8%) | 1,567 (60.3%) | 0.040 |
| African origin, n (%) | 0 (0.0%) | 150 (5.8%) | 0.029 |
| Body mass index (Kg/m²), mean ± SD | 31.4 (6.9) | 29.1 (6.7) | 0.003 |
| Smoking status, n (%) | 26 (33.3%) | 1,012 (38.9%) | 0.317 |
| Charlson comorbidity score, mean (SD) | 0.9 (1.5) | 0.5 (1.0) | 0.018 |

Abbreviations: AKN, acne keloidalis nuchae; n, number; SD, standard deviation.

Bold: significant value.

To the best of our knowledge, our study represents the first observational study aiming to shed light on the association between AKN and thyroid diseases. In previous studies assessing the relationship between thyroid and other dermatoses, a dominant motif in the connection between thyroid diseases and the skin is an inherent change to autoimmunity, which stems from thyroid ailments. While the exact etiology of AKN has yet to be determined, changes in autoimmunity have been reported as a contributing factor for AKN. This may provide insight into our findings regarding the association between AKN and hypothyroidism.

A scattered body of evidence has accumulated to suggest that endocrine and metabolic variables may play a role in the course of AKN. The skin’s ability to act as an endocrine organ and the emerging association of AKN with obesity and the metabolic syndrome may lend credibility to this assumption and account for, at least in part, the increased risk of hypothyroidism among patients with AKN.

The greater dominance of females among patients with AKN and thyroid diseases aligns with the general female preponderance in thyroid diseases and autoimmune thyroid disease, in particular. The latter observation was attributed, among other factors, to X chromosome inactivation and resultant tissue chimerism. The female-specific HR of hypothyroidism fell short of significance since owing to the small sample size of the female group, which renders the study underpowered to reveal significant differences. The higher burden of comorbidities in the group with coexistent AKN and thyroid diseases accords with
the well-established association of thyroid diseases with comorbid conditions.19,20

The current study throws light on important comorbidity which is yet to be investigated. Utilizing the largest cohort of patients with AKN, we were able to demonstrate an increased risk of hypothyroidism among patients with AKN relative to matched control subjects. The large-scale nature and the population-based setting of the study render it less susceptible to selection and ascertainment bias. The main limitation of the present study arises from the lack of morphological features and severity outcomes of both AKN and thyroid comorbidities. Being of computerized dataset origin, the current study did not follow the formal diagnostic criteria of the investigated diseases. However, the diagnoses of both AKN and thyroid diseases are based on the chronic diseases registry of CHS renowned for its high validity.21

In conclusion, an increased risk of new-onset hypothyroidism was found among patients with AKN. On the other hand, patients with AKN did not demonstrate a significantly increased risk of hyperthyroidism. Awareness of the increased burden of hypothyroidism may be of help for physicians managing patients with AKN. Screening for hypothyroidism may be considered in AKN patients with a suggestive clinical picture. Further research is necessary to delineate the pathomechanism underlying this observation.

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