Risk factors, clinical course and long-term prognosis in hidradenitis suppurativa: a cross-sectional study

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Summary

Background Hidradenitis suppurativa (HS) causes considerable morbidity. The long-term prognosis is of obvious interest to both patients and physicians. We conducted this study to determine the prognosis and risk factors in patients diagnosed with HS.

Objectives To describe the long-term prognosis and the clinical course of HS and its association to known risk factors.

Methods A postal follow-up survey with uncomplicated factual questions was conducted. As all of the patients were well acquainted with their long-standing disease, this was thought to be sufficient for meaningful results. All cases were diagnosed by a dermatologist. Overall, 212 patients diagnosed with HS between 1981 and 2001 were studied after a median follow-up period of 22 years (range 12–32).

Results The overall response rate was 71%/2%, with 60-8% (129/212) valid (fully completed) questionnaires. Remission was reported by 39-4% (50/127) and improvement by 31-5% (40/127). Unchanged severity was reported by 20-5% (26/127), and 8-7% (11/127) experienced worsening disease. Tobacco smoking was reported by 92-2% (119/129). Among nonsmokers, 40% (35/88) reported remission vs. 29% (17/59) of active smokers. A higher proportion of nonobese patients (45%) reported remission than obese patients (23%).

Conclusions We found that 39-4% of the sample reported remission of HS. Suspected risk factors appeared to influence the prognosis. Smoking and obesity were significantly linked to a lower rate of self-reported remission. The notion that lifestyle factors play a role in HS appears to be supported by this survey.

What’s already known about this topic?
- Hidradenitis suppurativa (HS) causes considerable morbidity.
- Smoking and obesity are suggested exogenous risk factors, and inheritance has an influence on development of HS.
- Some patients with HS experience remission.

What does this study add?
- Non smoking and nonobesity are linked to a better chance of remission from HS.
- In this cohort 39% of patients experienced remission.
- New long-term follow-up data describing the clinical course of HS are presented.
likely to have a major impact on the lives of patients, a suggestion that is supported by the therapeutic challenges presented by HS. Encouragingly, therapy is currently attracting renewed attention owing to new treatment opportunities. Data on the prognosis or natural evolution of the disease are nevertheless of great interest to all those involved.

Although long-term follow-up is common for malignant skin disease, knowledge of the natural course of most benign dermatological diseases remains sporadic, and the prognosis of only a few diseases has been systematically explored. Knowledge about the natural course of HS is limited to sporadic accounts and a paper from von der Werth and Williams. Their study was based on patients undergoing treatment at a dermatology department in Nottingham, U.K., and revealed interesting data regarding age of onset, disease duration, possible remission, family history, aggravating factors and the effects of the menstrual cycle and menopause on women with HS.

Subsequently, obesity and tobacco smoking have been identified as additional risk factors. Both factors have been linked to clinical disease severity, and it has been suggested that weight reduction in the obese may ameliorate HS. It has furthermore been implied that HS symptoms ameliorate spontaneously with age, and that some patients can become disease free over time. However, data are limited.

We have therefore conducted a long-term follow-up of patients diagnosed with HS, but not necessarily subsequently treated at our institutions, in order to describe the clinical course of HS in greater detail.

Patients and methods

Study design

A postal questionnaire based on long-term follow-up with simple factual questions was conducted, partly of retrospective character and partly of current relevance. All patients were initially diagnosed by a dermatologist, and the clear symptomatology and long experience of the patients polled was thought to provide data of acceptable quality. To increase response rates, nonrespondents were either sent reminders by mail or telephoned.

Participants

Eligible patients (n = 212) in two cohorts were identified: one Danish (n = 141) and one Dutch (n = 79). Patients were diagnosed with HS between 1981 and 2001, and identified through medical records. Patients were excluded when contact information was not available (n = 7) or if they had died (n = 13). Current contact details were retrieved in the host countries’ social security number systems, or the addresses were looked up in medical records and cross-checked with public telephone books.

There were 26 male and 186 female patients in the combined cohort (12.3% male), and the mean age was 52.1 years (95% confidence interval [CI] 50.8–53.2) at follow-up. The follow-up period was 12–32 years, with a median of 22 years.

Eligibility criteria and questionnaire

Patients were eligible if they had been diagnosed with HS by a qualified dermatologist and had a diagnosis recorded in their medical records.

A seven-page, 43-question questionnaire was mailed to the 212 eligible participants, with a paid-postage return envelope enclosed. Questions regarding primary outcome measures such as development of disease, smoking, weight/height and family history were considered central. Questionnaires were counted as complete when 80% of central questions and 50% of other questions were answered. HS has easily identifiable symptoms, and patients who were diagnosed with HS by a dermatologist were considered able to answer simple and factual questions regarding the evolution of their disease. A medical language expert and back translation were used, ensuring the best possible conformity in the questionnaire in English, Danish and Dutch.

No ethical approval for this study was necessary according Danish and Dutch law regarding the questionnaire. All data were anonymized before analysis.

Outcome measures

The outcome measures were basic data regarding remission, factors associated with remission and known risk factors. Self-reported remission (i.e. no inflammatory boils the last 6 months) was considered the primary end point, and was used in comparisons where possible. Regarding prognostic factors we chose dichotomous categorical measures: active smoking vs. non-smoking, obesity [body mass index (BMI) > 30] vs. non-obesity and family history vs. no family history. The obesity vs. nonobesity categorization was based on our recent study of morbidly obese patients experiencing amelioration of HS due to weight loss after bariatric surgery.

Statistics

Unless otherwise noted, all statistic calculations were performed using SPSS Statistics version 20 (IBM, Armonk, NY, U.S.A.) for Mac OS X. Results are presented as a percentage, or as a mean with 95% CI or SD where relevant. Comparing means was done assuming normal distribution where acceptable (n ≈ 50) and using relevant parametric tests (t-test or ANOVA). Regarding prognostic factors for remission, multivariate analysis was done by logistic regression. With remission as the dependent factor, we controlled for categorical factors – active smoking, obesity, familial disposition for HS, and sex – and age as a continuous variable.

Point prevalences for the samples are reported with 95% CIs. Rates were compared using the χ² test using 2 × 2 cross tabulation if possible.
In all comparisons $P < 0.05$ was considered significant. Effect size (ES) was calculated by hand as bias-corrected (Hedges) Cohen’s $d$, and was reported as either small, medium or large according to Hojat and Xu.20

**Results**

There was a response from $71.4\%$ of patients, yielding $60.8\%$ ($129/212$) complete questionnaires. Incomplete questionnaires were scrutinized and excluded if found to be $< 50\%$ complete. Nonrespondents ($28.8\%$) and participants denying ever having had a diagnosis of HS ($10.4\%$) amounted to $39.2\%$ of the total ($83/212$). No differences were found between the Danish and Dutch cohorts for basic characteristics such as age and sex.

Among the valid respondents ($n = 129$) there were $13$ men and $116$ women ($10.1\%$ male). Respondents were aged $30–86$ years ($mean = 53.7, 95\% CI 52.3–55.3$) (Table 1). Their BMI ranged from $18.3$ to $48.0$ kg m$^{-2}$ ($mean = 27.0, 95\% CI 26.1–27.9$). The year of diagnosis was in the range $1981–2001$ and the median was $1990$; hence, the shortest follow-up period was $12$ years, the longest period was $32$ years and the median was $1990$; hence, the shortest follow-up period was $12$ years, the longest period was $32$ years and the median and average follow-up period was $22$ years.

Generally, nonrespondents were younger than respondents, with a mean age of $49.4$ years ($95\%$ CI $47.6–51.4$). In comparison with responders the mean difference of $4.3$ years was significant ($P = 0.001$); however, the ES was only small to medium (ES $0.4$). The male-to-female ratio was $13:70$ ($16\%$ male) (Table 1). There was no significant difference in this ratio compared with responders.

### Disease characteristics in respondents

In the cohort, $38.0\%$ of patients ($49/129$) had a family history of HS defined as an affected first- or second-degree relative. Approximately two-fifths of respondents ($41.9\%$, $54/129$) indicated no familial disposition to HS, and $20.2\%$ ($26/129$) registered their familial disposition as unknown.

Symptomatic lesions were most frequently located in the groin ($47.2\%$, $60/127$) or genital area ($29.9\%$, $38/127$). Lesions in the axillae were reported by $25.6\%$ of patients ($32/125$) and inflammatory lesions by $12.0\%$ ($15/125$). More than one-third of the sample ($33.9\%$, $43/127$) had more than one affected region. Scarring was reported by $78\%$ ($67/86$) of respondents.

In describing the development of their disease, remission was reported by $39.4\%$ of patients ($50/127$) and improvement by $31.5\%$ ($40/127$). Only $20.5\%$ ($26/127$) considered their disease severity to be unchanged, and $8.7\%$ ($11/127$) indicated that their disease had worsened over time.

Patients reporting remission were generally older; their mean age was $55.8$ years ($95\%$ CI $53.4–58.3$). Patients who reported active disease had a mean age of $52.4$ years ($95\%$ CI $50.3–54.5$). The mean difference was $−3.5$ years ($P = 0.036$, ES $0.4$).

In general, once a region was affected it remained so. This was reported by $64.1\%$ ($66/103$) of patients, whereas $33.0\%$ ($34/103$) experienced activity in both established and new locations. Only $2.9\%$ (three of $103$) experienced total resolution in one location and activity in a new location.

Within the group of participants reporting cessation of disease activity ($39.4\%$, $50/127$), the age of disease resolution was $23–69$ years, with a mean of $41.8$ years ($95\%$ CI $38.7–45.0$).

Among patients indicating that they still suffered from active HS, $44\%$ ($32/73$) reported symptoms a few times a year; $32\%$ ($23/73$) monthly symptoms, $4\%$ (three of $73$) symptoms every week and $21\%$ ($15/73$) continuous activity.

### The effect of pregnancy and menopause

The majority of women ($72\%$, $61/85$) reported no effect of pregnancy on their HS, while $20\%$ ($17/85$) indicated amelioration and $8\%$ (seven of $85$) deterioration. Considering the influence of menopause on disease evolution, the majority of women ($48\%$, $29/61$) reported that menopause attenuated their symptoms. Some $38\%$ ($23/61$) felt no difference after menopause and $15\%$ (nine of $61$) indicated worsening of their HS following menopause.

### Risk factors and comorbidities

The lifelong incidence of tobacco smoking was $92.2\%$ ($119/129$). In this sample $45.7\%$ ($59/129$) were still active smokers, whereas $46.5\%$ ($60/129$) reported having stopped smoking and $7.8\%$ ($10/129$) had never smoked.

The most prevalent self-reported comorbidities were hypertension, acne and diabetes; however, the sample generally had a high prevalence of comorbidities, which are listed in Table S1 (see Supporting Information).

### Table 1 Respondent vs. nonrespondent characteristics

<table>
<thead>
<tr>
<th></th>
<th>Respondents</th>
<th>Nonrespondents</th>
<th>Whole cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>129 (60-8)</td>
<td>83 (39-2)</td>
<td>212 (100)</td>
</tr>
<tr>
<td>Age (years), mean (95% CI)</td>
<td>53.7 (52.3–55.3)</td>
<td>49.4 (47.6–51.4)</td>
<td>52.1 (50.8–53.2)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (10-1)</td>
<td>13 (16)</td>
<td>26 (12-3)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>116 (89-9)</td>
<td>70 (84)</td>
<td>186 (87-7)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Treatment

A majority (61·0%, 64/105) had used systemic antibiotics, and fewer (47%, 45/96) had been treated with topical antibiotics. A majority (77·2%, 95/123) also indicated that they had been treated with incision, whereas treatment with excision or deroofing had been used in 55·8% (63/113) or 57·7% (64/111), respectively.

Prognostic factors

Looking at the association between smoking and development of disease, 49% (33/68) of former smokers or nonsmokers were disease free, whereas only 29% (17/59) of the active smokers achieved remission (Fig. 1). Approximately two-thirds (66%, 33/50) who reported remission of disease were nonsmokers, whereas 34% were still smokers. The odds ratio (OR) for self-reported remission in nonsmoking participants was 2·8 (95% CI 1·3–6·3, P = 0·012).

The association between obesity and evolution of disease is illustrated in Figure 2. Nonobese participants had an OR for remission of 3·9 (95% CI 1·4–11·0).

HS remission was reported by 48% of those not describing familial disposition, whereas 33% of patients with a known first-degree relative with HS indicated remission of the disease (Fig. 3). For participants with no known familial disposition, the OR for remission was nonsignificant (OR 0·6, 95% CI 0·3–1·4).

When controlling for age, smoking and obesity, the OR was 0·95 (95% CI 0·9–1·00, P = 0·03). However, the OR is only slightly smaller than 1. Sex was not associated with remission (OR 3·7, 95% CI 0·9–14·3, P = 0·62).

Discussion

The long-term evolution or prognosis of any disease is of interest not only to patients, but also to the treating physicians, yet for most diseases data beyond a 5-year horizon are scarce. We have therefore reported results regarding the course of HS after a mean follow-up of 22 years. We found that 39·4% of the sample reported remission of HS during this
period. Previously suspected risk factors appeared to influence the chance of remission, as a majority of patients reporting remission also indicated that they had stopped smoking or had never smoked. We have previously shown that a 15% weight reduction in patients with BMI ≥ 30 ameliorates HS.\textsuperscript{16} Similarly, nonobesity was significantly linked to a higher rate of self-reported remission. Thus, the notion that lifestyle factors (i.e. nonsmoking and nonobesity) play a role in the development of many cases of HS appears to be supported by this survey. However, heredity may also play a role, as a familial disposition appeared to reduce the likelihood of remission, indicating that genetics may also be an important aetiological factor.

The role of tobacco smoking with regard to HS is subject of much speculation. König \textit{et al.}\textsuperscript{13} suggested smoking to be the triggering factor, but indicated no specific mechanism. In agreement with previous reports, in this study we found that >90% of those who responded to our survey were active or former smokers. In earlier studies smoking has been reported at rates of 70–90% in populations of patients with HS.\textsuperscript{15,18,21} Yet data on the possible beneficial effects of smoking cessation are rare. One study of de novo occurrence rates following surgery reported fewer or no new lesions following HS surgery when combined with smoking cessation.\textsuperscript{22}

Kurzen \textit{et al.}\textsuperscript{2} presented a host of potential mechanisms of cigarette smoking in the pathogenesis of HS. These include the selectively inhibitory effect of alkaloids on microorganisms, with the exception of \textit{Staphylococcus aureus}. Alkaloids appear to be able to trigger positive feedback promoting growth and proliferation of \textit{S. aureus}, thus changing the microbiome. This possible mechanism is contradicted by the low prevalence of \textit{S. aureus} found in HS lesions, although the preclinical evolution before symptoms occur may play a role. The prolonged secretion of nicotine in sweat is also mentioned as a possible cause. The effects of nicotine include epidermal hyperplasia, release of tumour necrosis factor-\textgreek{a}, promotion of follicular occlusion and reduced macrophage and lymphocyte activity.\textsuperscript{2} Tobacco smoke also contains polyaromatic carbohydrates, which may play a role in the development of HS.\textsuperscript{23,24}

Our findings therefore lend support to the importance of tobacco in the aetiology of HS. Surveys of disease severity have previously indicated a positive correlation between disease severity and smoking.\textsuperscript{10} The present survey indicates that the chance of remission may be greater in those who stop smoking. This effect was most conspicuous for patients of normal weight, but a similar trend was noticed even in overweight patients.

Obesity is another possible risk factor. The supporting data consist of surveys of patients from many populations, as well as a positive correlation between BMI and disease severity.\textsuperscript{10} In contrast to tobacco smoking, some evidence of a more dynamic association between BMI and HS has been published.\textsuperscript{16} Data therefore exist to suggest that obesity is linked to the likelihood of developing HS and the severity of HS, and that weight reduction may improve HS.\textsuperscript{16} The proposed underlying mechanisms include local factors on the surface of the skin due to the warm and humid milieu in the skin folds of obese patients, as well as shear forces from clothes and skin–skin contact.\textsuperscript{15,16} More general factors such as the association between obesity and chronic low-grade inflammation may also be involved.\textsuperscript{22}

Although statistically not significant, the genetic predisposition of patients may influence the prognosis of HS. Familial disposition to HS is commonly accepted, with approximately one-third of patients listing a positive family history of HS. Furthermore, some researchers have described an autosomal dominant inheritance pattern with a variable penetrance.\textsuperscript{23,24}

The molecular genetics of HS have been a topic of interest since the seminal identification of candidate genes by Wang \textit{et al.}\textsuperscript{25} in 2010. The authors reported mutations of genes regulating the transmembrane protein, \textgreek{g}-secretase. In some families loss-of-function mutations in \textgreek{g}-secretase seem to predispose for HS-like lesions.\textsuperscript{26} Miskinyte \textit{et al.} also reported associated mutations in the \textgreek{g}-secretase stabilizing protein nicastin.\textsuperscript{26} In contrast, Pink \textit{et al.} were only able to find these mutations in a minority of patients studied.\textsuperscript{27}

This survey indicates a trend towards a lower chance of remission in those patients who report HS in a first- or second-degree relative compared with patients with no family history. This may imply the importance of genetic factors in a subgroup of patients. Confounders such as smoking or obesity did not explain the findings, and patients indicating no family history of HS appeared to be more overweight and smoke more, supporting the suggestion that different subpopulations of HS may exist.\textsuperscript{28}

The validity of these observations obviously requires discussion. A postal questionnaire does not have the same reliability as a physical examination, yet it is suggested that the validity of self-reported disease evolution in a long-standing disease with such clear symptoms as HS may provide useful results. It is further hypothesized that the stringent inclusion criteria may have improved the validity of the observations. The initial diagnosis of HS was based on a physical examination by a dermatologist, and most of the patients had disease sufficiently severe to warrant not only specialist referral, but also outpatient management at a hospital over a period of time, indicating a high likelihood that they were well acquainted with their disease.

The validity of results is this study is further supported by the good response rates after a long follow-up period.\textsuperscript{29} The fact that the patients in this study were similar, although recruited from two different countries, also supports the soundness of the observations, as does the patient characteristics, which appear similar to those previously reported by von der Werth and Williams.\textsuperscript{9} The follow-up period in this study is longer and the age span among participants is wider, indicating that the results are more likely to be representative with regard to the full course of the disease. The results are also in agreement with some of the proposed associations reported in recent literature indicating a possible link to the pathogenesis of the disease.
The response rate in our study is comparable with that in similar studies.\textsuperscript{18,19,30} Response bias must nevertheless be considered, as it is generally accepted that persons with a particular symptom or condition are more likely to participate in studies related to that symptom or condition because of the relevance of the study to their lives.\textsuperscript{29} Accordingly, the response rate to an HS-oriented questionnaire is likely to be higher in a group that feels affected by HS symptoms, thus potentially overestimating the prevalence of active disease and underestimating the rate of remission in this sample.

The sample shows large heterogeneity regarding age and follow-up period. It does not describe the entire lifespan or even duration of disease for every patient. We therefore cannot know whether patients with full remission will experience recurrences in the future or whether the patients who had only 12 years of follow-up will achieve remission. Also, as we rely on self-reported outcomes for follow-up, uncertainties or imprecisions are likely. We have therefore interpreted the data conservatively.

References


Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website: Table S1. Self-reported prevalence of comorbidities in the cohort.