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REVIEW

Review of Comorbidities of Hidradenitis Suppurativa: Implications for Daily Clinical Practice

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ABSTRACT

Hidradenitis suppurativa (HS) is a chronic, recurrent skin inflammatory disease associated with a variety of comorbidities, like reduced quality of life, metabolic syndrome, sexual dysfunction, working disability, axial spondyloarthritis, inflammatory bowel disease, depression, and anxiety. Like psoriasis, HS

patients have been found to have higher risk of cardiovascular death and suicide risk. Clinicians should be informed about these comorbidities so that appropriate screening is implemented. All this evidence suggests that for such a chronic, multi-comorbid disease, the use of validated outcomes to assess severity and effect of treatment, along with the use of clinically important patient reported outcomes, is essential. The potential of available treatments to negatively and positively affect these comorbidities should also be taken into account when designing treatment strategies. This review provides an outline of important HS comorbidities with emphasis on possible implications for daily clinical practice.

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Key Summary Points

Hidradenitis suppurativa is a chronic, recurrent skin inflammatory disease associated with significant psychological burden, like reduced quality of life, depression, anxiety, and sexual dysfunction.

Important comorbidities include working disability, metabolic syndrome, inflammatory bowel disease and axial spondyloarthritis.

Hidradenitis suppurativa patients are at higher risk of cardiovascular death and suicide risk.

Appropriate screening in daily clinical practice should be implemented for early identification and evidence based treatment.

The use of validated outcomes for assessment of disease severity and treatment effect, along with the use of important patient reported outcomes, is essential.

INTRODUCTION

Hidradenitis suppurativa (HS), or acne inversa, is a chronic inflammatory skin disease characterized by recurrent inflammation and deep-seated lesions in apocrine gland-bearing intertriginous areas of the body that can be potentially scarring and debilitating [1–3]. Prevalence of HS varies widely from 0.03 to 8%, depending on the setting and methodology used [4]. Patients often experience long delays before an HS diagnosis is established [5]. HS typically develops between puberty and the age of 40 years, thus impacts individuals at working age [2]. It is known to have substantial impact on several general health-related and skin-specific quality of life domains [6, 7], is associated with a significant comorbidity burden [3]

and overall mortality, and is becoming more widely recognized as an inflammatory disease with a number of systemic implications, like psoriasis.

In a recent global patient survey it became evident that patients reported a high frequency of comorbidities and that they were dissatisfied with medical or procedural treatments in 45.9% and 34.5%, respectively [8]. For such a chronic, debilitating inflammatory skin disease it is important that clinicians are well informed on possible comorbidities that can have a significant impact. The aim of the review is to present an up-to-date overview of HS comorbidities, discuss their clinical significance and how they can be addressed meaningfully, and shape daily treatment decisions (Table 1). This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

INCREASED CARDIOVASCULAR (CV) DISEASE RISK

A meta-analysis of observational studies including 6174 HS patients and 24,993 controls detected significant association of HS with obesity, central obesity, active smoking, history of smoking, hypertriglyceridemia, low HDL, diabetes, and metabolic syndrome [9]. These associations were significant both in population HS patients and hospital HS groups, with hospital HS groups having uniformly higher odds ratios than the population HS groups. CV risk factors appear at a significantly higher rate in HS patients compared to controls. Increased CV risk is manifest even in patients identified in population samples. Obesity is also a well-established independent risk factor for HS with improvements in disease severity demonstrated after weight loss, like lower HS prevalence and severity, better long-term prognosis, spontaneous resolution of HS, flare reduction and reduced recurrence after CO₂ laser surgery [10–13].

In a cross-sectional study with 68 HS patients and 136 age- and sex-matched healthy control subjects, HS was significantly related to presence of carotid plaques and increased frequency

Table 1. Important HS comorbidities and their implications for daily clinical practice

Comorbidities	Clinical significance
Association with cardiovascular disease risk factors: obesity, smoking, hypertriglyceridemia, low HDL, diabetes, metabolic syndrome [9]	Need for screening for modifiable cardiovascular risks Avoid treatments with potential negative impact on cardiovascular disease risk factors, e.g., acitretin
Increased frequency of subclinical atherosclerosis [14]	Implement weight loss strategies
Increased risk of adverse cardiovascular outcomes [16]	
Association with slower income growth, higher risk of leaving the workforce, more total work loss days, higher annual total indirect costs and lower annual income [17–20]	HS patients have unmet disease management needs Major surgery in selected cases may improve activity and overall work impairment [21] Adalimumab significantly improved total work impairment compared to placebo [22]
Axial spondyloarthritis	HS patients with osteoarticular symptoms (low back pain, dactylitis) should be monitored for spondyloarthritis
Association with increased risk of spondyloarthritis [23]	
In axial spondyloarthritis patients disease activity score is independently associated with presence of HS [24]	Axial spondyloarthritis patients with HS may have higher disease activity
Significant associations of HS with CD and ulcerative colitis [25]	Consultation with gastroenterologists if HS patients have recurrent abdominal pain, chronic diarrhea, bloody stool, or body weight loss
HS patients are at risk for CD [26]	
Reduced quality of life, social isolation [28, 29]	Development of strategies to recognize and treat those psychiatric comorbidities in patients with HS is warranted
Sexual dysfunction [31]	
Depression, anxiety, schizophrenia [29, 34, 35]	
Increased antidepressant drug use [36]	
Increased suicide risk [36]	
Syndromic HS: [36]	Lack of response to standard treatment modalities
PAPA: pyoderma gangrenosum, acne, pyogenic arthritis	Early identification is critical in order to optimize management
PASH: pyoderma gangrenosum, acne, and HS	
PAPASH: pyoderma gangrenosum, acne, pyogenic arthritis, and HS	
Other	Older patients, smokers, and patients with depression may benefit from periodic screening for long-term opioid use
Long-term opioid use [38]	
Psoriasis [39], pyoderma gangrenosum [40]	
Alopecia areata [40], vitiligo [41]	
rheumatoid arthritis [40], non melanoma skin cancer [42]	
<i>HS hidradenitis suppurativa, CD Crohn's disease</i>	

of subclinical atherosclerosis [14]. In a cross-sectional Danish general population study, mean resting heart rate in patients with severe HS was significantly higher compared with controls [15]. A population-based cohort study using individual-level linkage of nationwide administrative registers indicated that HS was associated with a significantly increased risk of adverse CV outcomes and all-cause mortality independent of measured confounders [16]. Notably, the risk of CV death was 58% higher in patients with HS than in patients with severe psoriasis.

These results emphasize the need for screening of HS patients for modifiable CV risk factors and consideration of them when deciding treatment options. For example, acitretin would be better avoided as a treatment for an HS patient with dislipidemia, since an abnormal lipid profile is a well-known potential side effect. Weight gain is a usual side effect of hormonal treatment (ethinylloestradiol and cyproterone acetate), especially with long-term use. Pre-treatment screening should be performed where necessary. Furthermore, weight reduction strategies appear to be beneficial and should be implemented.

WORKING DISABILITY

HS has been demonstrated to have a significant impact on patients' work productivity and negatively affect opportunities for career advancement. In a Polish survey of employed patients with HS, 58% reported that the disease caused a work absence with a mean 33.6 days off work annually, 10% reported that they lost their job because of HS and 23% believed that HS interfered with promotion [17]. In addition, patients with HS experience a substantial economic burden, with the total direct healthcare costs of patients with HS estimated to be \$6783 higher compared to those of controls over a 3-year period [18]. Higher total work productivity impairment scores compared to psoriasis were reported for HS [19]. In a US claims database analysis, newly diagnosed HS patients had significantly slower income growth and higher risk of leaving the workforce compared with

controls. General HS patients had more total work loss days, higher annual total indirect costs, and lower annual income compared with controls [20].

This evidence clearly indicates that HS patients have unmet disease management needs with respect to working disability. A single center prospective survey study conducted among 40 patients undergoing major surgery suggested that, after major surgery activity, overall work impairment showed considerable improvement [21]. Individual patient data from two phase 3, randomized, double-blinded studies, PIONEER I and II, and their open-label extension (OLE) trial were used to compare patients with moderate to severe HS treated with adalimumab or placebo [22]. Patients with HS receiving adalimumab experienced significantly lower cumulative indirect costs and significant improvement in total work impairment compared to placebo [22].

AXIAL SPONDYLOARTHRITIS

A single center cross-sectional study showed that HS was significantly associated with an increased risk of spondyloarthritis, independently of age and sex [23]. A cross-sectional study using a cohort of axial spondyloarthritis patients identified that HS was more prevalent than in the general population and that a higher score on axial spondyloarthritis disease activity score was independently associated with HS [24].

Patients with HS presenting osteoarticular symptoms, especially low back pain or dactylitis, should be monitored for spondyloarthritis. Furthermore, axial spondyloarthritis patients with HS may have higher disease activity.

INFLAMMATORY BOWEL DISEASE

A recently published meta-analysis of observational studies clearly showed significant associations of HS with Crohn's disease (CD) and ulcerative colitis (UC) [25]. Cross-sectional analysis of data from 51,340 patients with HS, identified using electronic health records data,

suggested that HS patients are at risk for CD and that prevalence of CD was greatest among patients with HS who were white, aged 45–64 years, non-obese and tobacco smokers [26]. High HS prevalence has been detected in patients with perianal fistula [27].

In patients with chronic perianal and perineal HS, and in particular in the presence of fistulas, the possibility of CD should be considered. Consultation with gastroenterologists should be sought when patients with HS present with recurrent abdominal pain, chronic diarrhea, bloody stools, and body weight loss. Early detection of the coexistence can lead to appropriate anti-inflammatory treatment to reduce symptoms and disease progression.

PSYCHOLOGICAL COMORBIDITY

Psychological comorbidities are well established and proven in HS patients. It was suggested that more than 50% of HS patients experience a very or extremely large effect of HS on quality of life, as measured by the Dermatology Life Quality Index (DLQI) [28]. Using EuroQoL-5D and DLQI scores it was found that HS is in the top five skin diseases with the most negatively affected quality of life and that predictive factors were young age at onset and more lesions per month [29]. DLQI was significantly worse in females compared to males. Quality of life in HS patients was found to be more negatively impacted than in psoriasis, acne, stroke, or heart transplant candidates [28].

It was found that HS has a great emotional impact on patients and promotes isolation due to fear of stigmatization [30]. Body image dissatisfaction may result in feelings of shame, embarrassment, and anxiety and cause lack of self-confidence, depression, and social isolation. Shame and irritation are frequent and relate to smell, scars, itching, and pain [30, 31].

Significant impairment of sexual health has also been clearly indicated in HS patients compared with age-, sex-, and BMI-matched controls, with women affected more than men [28]. Sexual health was impacted in HS due to inconvenience caused by skin inflammation, physical appearance, diminished sexual desire,

fear of passing HS on to children and diminished desire of partner [31]. Risk factors for sexual dysfunction for women were education status, disease activity, pain and odor, and lack of a stable relationship; and for men the risk factors were increasing age, active genital lesion and number of active areas [32, 33]. These results reinforce the need to take sexual health into account when assessing disease severity, response to treatment, and patient goals of care.

A recent meta-analysis of the literature suggested that depression and anxiety were very common comorbid conditions in HS patients. Depression was found to be correlated with disease activity and an association between inflammation (CRP levels) and depression has also been identified [29, 34]. Recent evidence from a nationwide population-based study suggested that HS was associated with schizophrenia, after adjusting for demographic factors and smoking status [35].

Taking into account all the abovementioned evidence, it is no surprise that data from a cross-sectional and cohort study, using Danish national registries, found that patients with HS compared with the general population had an increased risk of antidepressant drug use, completed suicides and suicidal behavior, and that this increased risk of completed suicide remained, after adjustment for confounding factors [36].

SYNDROMIC HS

Syndromic HS exists as well. Autoinflammatory syndromes associated with hidradenitis suppurativa (HS) and/or acne are rare but potentially debilitating disorders. Several clinically different syndromes exist including pyoderma gangrenosum, acne, and pyogenic arthritis (PAPA), pyoderma gangrenosum, acne, and hidradenitis suppurativa (PASH), pyoderma gangrenosum, acne, pyogenic arthritis, and hidradenitis suppurativa (PAPASH), psoriatic arthritis, pyoderma gangrenosum, acne, and hidradenitis suppurativa (PsAPASH) and pyoderma gangrenosum, acne and ulcerative colitis (PAC) [37].

Important features in these syndromes are painful arthritis, skin lesions (HS, acne and pyoderma gangrenosum) and recurrent episodes of fever. Treatment can be challenging due to lack of response to standard treatment modalities. Early identification is critical in order to optimize management.

OTHER COMORBIDITIES

A retrospective cohort study showed that HS patients were at higher risk for long-term opioid use [38]. Older patients, smokers, and patients with depression were at higher risk for opioid abuse. Evidence suggests that this subgroup of patients may benefit from periodic screening for long-term opioid use.

Association with psoriasis [39], alopecia areata [40], vitiligo [41], pyoderma gangrenosum, rheumatoid arthritis, and non-melanoma skin cancer [42] have also been suggested as comorbid diseases.

DISCUSSION

The abovementioned evidence clearly indicates that HS is a multifaceted disease with many different comorbidities that, if not identified early and treated properly, can result in a significant burden for HS patients and society. In order to cope with such a disease it is of high importance to use validated outcomes to assess the severity of the disease and treatment effect.

IHS4 is a validated tool to dynamically assess HS severity and can be used both in real life and in a clinical trials setting. The IHS4 score is calculated by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4–10 signifies moderate, and 11 or higher signifies severe disease. This correlates well with the Hurley classification, Expert Opinion, Physician's Global Assessment, Modified Sartorius score, and DLQI [43].

HiSCR (hidradenitis suppurativa clinical response) is defined as $\geq 50\%$ reduction in

inflammatory nodule and abscess count and no increase in number of abscesses or draining fistulas compared with baseline [44]. The use of HiSCR is supported by good-quality validation studies, and is recommended to be used as a dichotomous outcome measure to assess the effects of anti-inflammatory treatment [44]. A post hoc analysis of integrated data from two phase 3 clinical trials (PIONEER I and II) revealed that more HiSCR responders than non-responders experienced clinically meaningful improvement in the Dermatology Life Quality Index, Pain Numeric Rating Scale, HS quality of life, work-related performance, and non-work-related performance. Clinically meaningful outcomes in HS are more likely to be attained in patients achieving HiSCR-level improvement.

Patient-reported outcome measures [e.g., DLQI, Numerical Rating Scale (NRS)] should be included in the overall assessment of the HS patient as they may offer important insight on functioning, quality of life, and symptoms (e.g., pain and itching), especially when the minimum clinically important differences for such outcomes is used, like at least a four-unit decrease in DLQI score and $\geq 30\%$ reduction in NRS pain score.

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