Hidradenitis suppurativa

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DOI:
10.33612/diss.119123035

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IDENTIFICATION OF CLINICAL CATEGORIES IN HIDRADENITIS SUPPURATIVA BASED ON PATIENT CHARACTERISTICS: RESULTS FROM A CLUSTER ANALYSIS

In preparation

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ABSTRACT

Background: It is suggested that hidradenitis suppurativa (HS) is a skin disease with a certain phenotypic heterogeneity, which possibly indicates different etiologic, pathophysiologic and genetic backgrounds that require tailored treatment approaches. Robust description of HS phenotypes does not yet exist.

Objectives: To identify distinct clinical categories of HS patients based on associated clinical patient characteristics.

Methods: Cross-sectional study. Cluster analysis was performed on two prospective, longitudinal and observational cohorts including adult HS patients seen in three centres in the Netherlands between 2015 and 2017. Clinical variables included in the analysis were sex, smoking history, body mass index (BMI), and follicular occlusion comorbidity.

Results: Included were 345 HS patients: 72.8% female, mean age 38.3 ± 12.2 years, mean symptom duration 15.4 ± 11.7 years, mean BMI 29.0 ± 6.3 kg/m^2, and 82.3% was ever a smoker. Five distinct clinical sub-categories of HS were revealed: cluster 1. "females with stereotypical HS" (40.0%) are characterized by female smokers with overweight; 2. "females with a single exogenous risk factor for HS" (22.6%) is marked by females that either have a positive smoking history or are overweight; 3. "male HS" (22.0%) represents male patients who have a positive smoking history and/or are overweight; 4. "HS plus follicular occlusion comorbidity" (n=32, 9.2%) is defined by HS patients who are also known with acne conglobata, dissecting cellulitis of the scalp and/or pilonidal sinus; and 5. "limited HS" (6.1%) typifies HS patients without associated risk factors smoking, high BMI and follicular occlusion tetrad comorbidities.

Conclusion: These clinical sub-categories of HS may help to define sound phenotypes of HS.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, painful, immune mediated auto-inflammatory skin disease affecting approximately 1% of the general population.[1,2] Hidradenitis suppurativa is located typically in the inverse body regions like axillae, inframammary, inguinofemoral region, perineal regions, and buttocks. Ectopic sites such as the face, neck, and abdomen can also be involved.[1,2] The exact pathophysiology and possibly underlying genetic cause remain uncertain. Current scientific insight shows that the first pivotal histological event in HS is hyperplasia and hyperkeratosis of the follicular infundibulum that leads to follicular plugging. This eventually results in rupture and incitement of a perifollicular aberrant inflammatory response causing typical deep-seated inflammatory nodules.[3] Other (frequently) seen elements are abscesses, sinus tracts, 'tombstone' double-ended or giant comedones (pseudocomedones) and hypertrophic 'bridged' and 'crater holes' scars.[4] Identified risk factors for HS are female sex, high body mass index (BMI), and smoking.[2,5] Hidradenitis suppurativa has been described as part of syndromes, particularly the follicular occlusion tetrad (HS, acne conglobata, dissecting cellulitis of the scalp and pilonidal sinus). It is thought that these comorbidities share a similar (histo)pathophysiology.[6] Furthermore, HS is associated with other (auto-)inflammatory diseases, such as Crohn's disease and spondyloarthropathy.[6–9] The clinical spectrum of HS disease is wide, ranging from subclinical and mild to very severe symptoms. Symptoms can relapse, be continues for a long period, and go in remission. It is therefore suggested that HS is a disease with a phenotypic heterogeneity possibly indicating different etiologic, pathophysiologic and genetic backgrounds that require tailored treatment approaches.[10,11] Propositions for categorization of HS into clinical phenotypes have been published previously (Table 1).[12–15] Furthermore, several authors have described distinct morphological presentations of HS in some patients, such as "plaque form" and "ectopic" or "atypical" HS.[16–20] However, all of these categorizations have not been internationally accepted thus far and the genetic and pathophysiological background was not investigated. This necessitates further investigation to understand many aspects of HS disease such as aetiology and pathophysiology, to ultimately enhance treatment outcomes. Towards valid identification of HS phenotypes, categorization of HS patients based on associated patient characteristics will be valuable.[11] Therefore, in this study we sought to investigate distinct clinical categories of HS based on clinical patient characteristics.

Table 1. Previously proposed clinical phenotypes in hidradenitis suppurativa

Author, year of publication, and study design	Subgroup/Phenotype	Description
Canoui-Poitrine et al., 2013[12] Cross-sectional, latent class analysis, n=618	Axillary–mammary (48%)	Predominant locations are the axillae and breast. Predominant lesions are hypertrophic scars. More likely female sex, less likely smokers, less likely to have family history.
	Follicular (26%)	Predominant locations are the axillae or breast, ears, chest, back, and legs. Predominant lesions are follicular lesions such as comedones, epidermal cysts, and pilonidal sinus. Other characteristics are a history of severe acne, family history of HS, higher proportion of men and current/former smokers, greater disease severity (Sartorius and Hurley), earlier disease onset, and longer disease duration.
	Gluteal (26%)	Predominant location is the gluteal area. Predominant lesions are papules and folliculitis. Other characteristics are a family history of HS, higher proportion of smokers, lower BMI values, less severe disease, longer duration.
Van der Zee and Jemec, 2015[13] Expert opinion, descriptive, n=0	Regular	Fulfilment of all diagnostic criteria for HS, most common type, all patients who lack other specific characteristics belong in this group.
	Frictional furuncle	Predominant affected locations are sites that are exposed to enhanced friction, such as abdomen, thighs and buttocks. Predominant lesions are multiple deep nodules and abscesses. Sinus tract formation is unusual. Other characteristics are being overweight.
	Scarring folliculitis	Buttocks, inguinal area, and pubic area are predominantly affected. Predominant lesions are pustules, cysts, superficial nodules, depressed cribriform scarring, double-ended comedones. Sinus tract formation is unusual. Other characteristics are being overweight and smoker.
	Conglobata	Back and face are predominantly affected. Predominant lesions are cysts and sinus tracts. Other characteristics are acne conglobata, family history of HS, overweight, and male sex.
	Syndromic	Patients are characterized by concomitant diseases, such as pyoderma gangrenosum and arthritis, such as the pyoderma gangrenosum, acne, and suppurative hidradenitis (PASH) syndrome or pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis (PAPASH) syndrome.
	Ectopic	HS involving the face.
Theut Riss et al., 2017[14] Explorative, cross-sectional, descriptive study, n=451	Low BMI (<25 kg/m^2)	Less severe disease (based on Hurley classification, physician global assessment, number of areas affected and patient-reported severity)
	High BMI (>25 kg/m^2)	More severe disease (based on Hurley classification, physician global assessment, number of areas affected and patient-reported severity). No difference in smoking or family history of HS.
Frew et al., 2019[15] Explorative, descriptive, n=0	Typical	Similar to the previously described "axillary–mammary" type by Canoui Poitrine *et al*. and "regular" type by Van der Zee and Jemec.
	Atypical	This includes two subtypes: - Scarring follicular subtype. Similar to the previously described "follicular" and "gluteal" type by Canoui Poitrine *et al*. and "scarring folliculitis by Van der Zee and Jemec. - Conglobata subtype. Similar to the previously described "follicular" and "gluteal" type by Canoui Poitrine *et al*. and "conglobata" type by Van der Zee and Jemec.
	Syndromic	Not strictly defined, but might include PASH (pyoderma gangrenosum, acne and HS) and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne and HS) syndromes, and maybe autoimmune, inherited and autoinflammatory syndromes (such as familial Mediterranean fever, Crohn's disease, and Dowling-Degos disease).

METHODS

Patients

In this cross-sectional study, baseline data of all patients with HS from in the Hidradenitis Suppurativa Registry (HiSURE) cohort of the University Medical Center Groningen (UMCG) between April 2015 and July 2017 and the Hidradenitis suppurativa CARE (HiCARE) cohort of the UMCG, Meander Medical Hospital (Amersfoort) and Hospital Nij Smellinghe (Drachten) in the Netherlands between March 2018 and June 2019 were included. Both cohorts are prospective, longitudinal and observational cohorts in which all consecutive adult HS patients clinically diagnosed by a dermatologist (based on the modified Dessau definition of HS), who are cognitively able and willing to participate, are included and data is collected in a standardized manner.

In both cohorts, variables are recorded in a standardized manner, which include sex, smoking history, body mass index (BMI), age at symptom onset, family history of HS, comorbidities such as the history or present occurrence of severe acne/acne conglobata, pilonidal sinus and dissecting cellulitis of the scalp, and symptoms of HS at baseline. Presence of comedones and refined Hurley stage was standardly recorded in the HiCARE study. In the HiSURE cohort, presence of comedones and refined Hurley stage was retrieved retrospectively by reviewing written medical records and photo documentation.

Statistical analysis

Descriptive statistics were used to describe the study population. Results are presented as number of patients (%), mean ± standard deviation, or median (interquartile range) for categorical, normally distributed and non-normally distributed data, respectively. Hierarchical cluster analysis with a Ward minimum-variance and agglomerative approach is performed to explore whether different clusters, i.e. phenotypes, within the HS disease spectrum can be defined.

Four variables, all made binary, were critically chosen for the analysis because they are considered as significant determinants of the HS clinical phenotypes: sex categorized in female and male, smoking history categorized in never smoked and current/former smoker, BMI categorized in underweight plus normal (<25 kg/m^2) and overweight plus obese (≥25 kg/m^2), and presence of the follicular tetrad comorbidities: acne conglobata, pilonidal sinus and dissecting cellulitis of the scalp categorized in none and ≥1 present in the patient. Symptoms of HS, such as presence of inflammatory nodules, abscesses, sinus tracts, comedones, scarring, inflammation, and number of involved body regions were not included as variables, as these symptoms can be considerably inconsistent over time and can be quite difficult to assess.

The output of the cluster analysis is a dendrogram: a diagram that represents a tree in which each subject starts as a single cluster and then joins subjects who are closest to each other based on similarities or dissimilarities and these initial clusters are then merged according to the similarities and so on until all subjects form one cluster. Cut-off points in the dendrogram were determined based on the formation of the clinically most relevant phenotypes.

Group comparisons between all clusters were performed using one-way ANOVA for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables or Chi-square test for categorical variables. In case the overall group comparison was statistically significant, independent sample t-test, Mann-Whitney U test, and Chi-square test or Fisher's exact test were performed as appropriate to compare between the individual clusters.

Statistical analysis was performed using IBM SPSS Statistics 23.0 for Windows (SPSS, Chicago, IL, USA). P-values ≤0.05 were considered statistically significant.

RESULTS

In total, 345 HS patients were included (HiSURE 65.8%; HiCARE 34.2%). Of these, 72.8% were female, mean age was 38.3 ± 12.2 years, mean symptom duration was 15.4 ± 11.7 years, mean BMI was 29.0 ± 6.3 kg/m², and 82.3% was ever a smoker (Table 2). These patient characteristics were similar in both cohorts (HiSURE and HiCARE).

Cluster analysis

Interpretation of the cluster analysis results revealed five categories (Table 2 and 3).

The largest group, cluster 1 (n=138, 40.0%) was designated as "females with stereotypical HS". This category included solely females who all present with a positive smoking history (former or current) and obesity (mean BMI 32.6 ± 5.9 kg/m²). All refined Hurley stages were seen, similar to the entire cohort. About half of these patients presented with sinus tracts and/or comedones. Conjunction of follicular occlusion tetrad comorbidities was not seen in this cluster. Cluster 2 (n=78, 22.6%) was named "females with a single exogenous risk factor for HS" and represents females that are either former/current smokers (73.1%) or are overweight/obese (26.9%)). Like in cluster 1, follicular occlusion tetrad comorbidities were not present. Cluster 3 (n=76, 22.0%), was defined as the "male HS" type and represents a cluster formed by only males, that had similar characteristics as the entire HS study population. In this group, 75% had sinus tracts (thus presented with either refined Hurley stages IIA, IIB and IIC or III). Comedones were seen in half of the patients. Similar to cluster 1 and 2, follicular occlusion tetrad comorbidities were not present. Cluster 4 (n=32, 9.2%) represents the "HS plus follicular occlusion comorbidity" category.

Table 2. Demographic characteristics of the overall cohort and of the separate categories

	Overall population, n=345	Cluster 1, n=138 (40.0) "Females with stereotypical HS"	Cluster 2, n=78 (22.6) "Females with a single exogenous risk factor for HS"	Cluster 3, n=76 (22.0) "Male HS"	Cluster 4, n=32 (9.3) "HS plus ≥1 other follicular occlusion disease"	Cluster 5, n=21 (6.1) "Limited HS"	Overall comparison between all clusters, p-value
Sex							<0.001[b-j]
Male	94 (27.2)	0 (0)	0 (0)	76 (100)	15 (46.9)	3 (14.3)	
Female	251 (72.8)	138 (100)	78 (100)	0 (0)	17 (53.1)	18 (85.7)	
Smoking							<0.001[a-e,g,i,j]
Never	61 (17.7)	0 (0)	21 (26.9)	10 (13.2)	9 (28.1)	21 (100)	
Former or current	284 (82.3)	138 (100)	57 (73.1)	66 (86.8)	23 (71.9)	0 (0)	
BMI							<0.001[a-g,i,j]
< 25 kg/m^2	101 (29.3)	0 (0)	57 (73.1)	16 (21.1)	7 (21.9)	21 (100)	
≥ 25 kg/m^2	244 (70.7)	138 (100)	21 (26.9)	60 (78.9)	25 (78.1)	0 (0)	
Follicular occlusion tetrad comorbidities*							<0.001[c,f,h,j]
No	313 (90.7)	138 (100)	78 (100)	76 (100)	0 (0)	21 (100)	
Yes	32 (9.3)	0 (0)	0 (0)	0 (0)	32 (100)	0 (0)	
Age, *years*	36.0 (28.0-48.0)	39.0 (32.0-47.0)	33.5 (26.0-48.0)	36.0 (29.0-51.0)	32.0 (28.0-41.0)	27.0 (21.8-45.0)	0.026[c,d,i]
Symptom duration, *years*	12.0 (6.0-22.0)	15.5 (8.0-24.3)	11.0 (6.0-20.0)	11.0 (6.0-22.0)	12.0 (6.3-20.8)	5.0 (2.0-18.3)	0.001[d,i,j]
Age at onset of HS symptoms, *years*	20.0 (15.0-28.0)	20.0 (15.0-28.0)	20.0 (15.0-27.0)	23.0 (17.0-31.0)	18.5 (15.0-25.8)	19.0 (16.5-24.8)	0.660
BMI exact, *kg/m^2*	27.6 (24.5-33.0)	32.0 (27.4-35.7)	23.8 (21.2-26.4)	27.6 (25.3-30.4)	29.5 (25.2-32.3)	23.3 (22.0-24.2)	<0.001[a-f,i,j]
Family history HS in 1st degree							0.186
No	231 (67.0)	88 (63.8)	55 (70.5)	52 (68.4)	18 (56.3)	18 (85.7)	
Yes	114 (33.0)	50 (36.2)	23 (29.5)	24 (31.6)	14 (43.8)	3 (14.3)	
Refined Hurley							0.002[a,d,i]
Stage IA	75 (21.7)	22 (15.9)	24 (30.8)	10 (13.2)	7 (21.9)	12 (57.1)	
Stage IB	27 (7.8)	15 (10.9)	3 (3.8)	5 (6.6)	3 (9.4)	1 (4.8)	
Stage IC	32 (9.3)	20 (14.5)	5 (6.4)	4 (5.3)	2 (6.3)	1 (4.8)	
Stage IIA	34 (9.9)	11 (8.0)	12 (15.4)	7 (9.2)	2 (6.3)	2 (9.5)	
Stage IIB	64 (18.6)	24 (17.4)	16 (20.5)	15 (19.7)	8 (25.0)	1 (4.8)	
Stage IIC	87 (25.2)	40 (29.0)	14 (17.9)	25 (32.0)	6 (18.8)	2 (9.5)	
Stage III	26 (7.5)	6 (4.3)	5.1 (5.1)	10 (13.2)	4 (12.5)	2 (9.5)	
Sinus tract formation							0.009[b,d,e,g,i,j]
No	134 (38.8)	57 (41.3)	32 (41.0)	19 (25.0)	12 (37.5)	14 (66.7)	
Yes	211 (61.2)	81 (58.7)	46 (59.0)	57 (75.0)	20 (62.5)	7 (33.3)	
Comedones							0.005[a,d,e,i]
No	174 (50.4)	58 (42.0)	48 (61.5)	34 (44.7)	18 (56.3)	16 (76.2)	
Yes	171 (49.6)	80 (58.0)	30 (38.5)	42 (55.3)	14 (43.8)	5 (23.8)	

Results are presented as number of patients (%), mean ± standard deviation or median (interquartile range).

HS, hidradenitis suppurativa; BMI, body mass index.

a. p<0.05 when comparing cluster 1 to cluster 2; b. p<0.05 when comparing cluster 1 to cluster 3; c. p<0.05 when comparing cluster 1 to cluster 4; d. p<0.05 when comparing cluster 1 to cluster 5; e. p<0.05 when comparing cluster 2 to cluster 3; f. p<0.05 when comparing cluster 2 to cluster 4; g. p<0.05 when comparing cluster 2 to cluster 5; h. p<0.05 when comparing cluster 3 to cluster 4; i. p<0.05 when comparing cluster 3 to cluster 5; j. p<0.05 when comparing cluster 4 to cluster 5.

* Acne conglobata, dissecting cellulitis of the scalp, and/or pilonidal sinus.

Table 3. Description of categories according to this cluster analysis study

Cluster	Category	Sex	Smoking	BMI	Follicular occlusion tetrad	Sinus tracts	Comedones	Symptoms duration
1	Female stereotypical HS	♀	+	+	-	↑↓	↑↓	↑
2	Females with single exogenous risk factor for HS	♀	+/-	+/-	-	↑↓	↓	↑↓
3	Male HS	♂	+/-	+/-	-	↑	↑↓	↑↓
4	HS plus ≥1 other follicular occlusion disease	♀/♂	+/-	+/-	+	↑↓	↑↓	↑↓
5	Limited HS	♀/♂	-	-	-	↓	↓	↓

HS, Hidradenitis suppurativa; BMI, Body mass index.

Besides having HS, all of these patients also had a history of pilonidal sinus, acne conglobata or dissecting cellulitis of the scalp. The final cluster is number 5 (n=21, 6.1%). This category does not present with HS risk factors, smoking, overweight/obesity, or follicular occlusion comorbidities. Therefore, this cluster is termed the "limited HS" category.

Clinical characteristics

Comparison of patient characteristics of the first category "females with stereotypical HS" to the other 4 categories particularly showed a higher BMI (median 31.97 (27.43-35.73) vs. 23.26 (21.99-24.22) to 29.47 (25.17-32.29), $p<0.05$). Presence of comedones was seen significantly less in "females with a single exogenous risk factor for HS" (38.5%), compared to "females with stereotypical HS" and "male HS" (58.0% and 55.3%, respectively). Patients belonging to the "limited HS" category presented at a significantly younger age compared to category 1 and 4 and have significantly shorter symptom duration compared to all other phenotypes except category 2 ("female with a single exogenous risk factor for HS") ($p<0.005$). Furthermore, a large proportion of refined Hurley stage IA stage (57%), especially compared to the "female stereotypical HS" category and "male HS" category, was seen in this category (15.9% and 13.2%, respectively, both $p<0.05$). Sinus tract formation is seen significantly less in this category compared to all other categories. Presence of comedones were also seen less in this category, again particularly compared to the "female stereotypical HS" phenotype and the "male HS" type ($p<0.05$). For age at onset of HS symptoms and family history of HS no statistical significant difference were found when comparing all clusters at once. To avoid bias of multiple testing, these variables were not further tested between single clusters.

DISCUSSION

In the present study using data from two prospective observational HS patient cohorts, we identified five distinct clusters, i.e. clinical categories, within the HS disease spectrum (Table 3). Cluster analysis was performed with the clinically known relevant variables sex, smoking history, BMI and follicular occlusion tetrad comorbidities. These variables were carefully chosen by HS experts based on a sizeable body of evidence from former studies supporting the importance of these risk factors and comorbidities.[6]

The largest category that we identified is the "female stereotypical HS" cluster which describes the classic HS patient: a smoking, obese, female patient. As the name implies, the second largest category "females with single exogenous risk factor for HS", also concerns females, but in contrary to the first category these patients are only exposed to one exogenous risk factor (either current/former smoker or BMI >25 kg/m2). In this second category, comedones are seen less frequently than in the first (and third) phenotype, which might indicate the importance of exogenous risk factors in contributing to comedone formation. In contrary to the first two categories, which include solely females, the third category consists exclusively of males. Sinus tracts are frequently seen in this group. Other patient characteristics are similar to the overall HS population.

In all the first three clusters, sex and exogenous risk factors smoking and BMI define the category. Epidemiologically, female sex is an important risk factor for HS as HS affects three times as many women as men.[1] Observational data shows that onset of HS usually occurs after puberty, pre-menstrual flares are reported, and disease activity might become less during pregnancy and worsens post-partum.[21] In general, as learned from previous research, sex should be considered as an important biological variable in fundamental, preclinical, and clinical research of HS.

Cigarette smoking (former/current) and being overweight or obese have shown to be the two most important recognized exogenous risk factors for developing HS and worse disease outcome, because they induce alteration of inflammatory responses and histological changes.[3,22,23] It seems almost self-evident that treatment strategies targeting life style intervention, i.e. behavioural changes to achieve normal body weight and cessation of smoking, need to be applied for to achieve better HS disease outcome.

Nearly one out of ten patients in this study were grouped into the fourth category "HS plus ≥1 other follicular occlusion disease", which concerns HS patients with acne conglobata, pilonidal sinus and/or dissecting cellulitis of the scalp. Patients of this group seem to be somewhat younger at initial HS symptom onset, although not confirmed statistically. All conditions in this tetrad (including HS) share the contributing aetiological factor of follicular occlusion. However, much more than this shared pathogenesis remains unknown. Importantly, treatment modalities for patients in this group might differ from

the other categories. For example, treatment with systemic retinoid might be more effective and therefore should be higher up the treatment ladder. However, this needs further investigation.

Strikingly, this analysis also revealed a group of patients who are not exposed to any typical exogenous risk factors (i.e. smoking and overweight) for HS. We designated this category as "limited HS". More than half of these patients presented with a Hurley stage IA. Accordingly, sinus tracts are less frequently seen in this category when comparing to the other categories. These patients have a shorter duration of HS symptoms. It would be very interesting to further study patients within this category to try to uncover why and how they developed HS and what their clinical course will be. This might generate more data about risk factors and the pathophysiology of HS for instance.

This study is not the first in a quest to identify HS categories, subtypes or phenotypes within the HS disease spectrum (Table 1). However, this is the first attempt to identify distinct categories based on clinical data using cluster analysis. This statistical technique can be used to make relatively homogenous groups out of heterogeneous variables. It is said to be an unsupervised and unbiased method, however, the choice of variables included in the analysis may influence the results. Moreover, cluster analysis cannot distinguish between possibly important or unimportant variables. As said before, the variables used in this study were critically chosen based on scientific evidence and clinical relevance in HS.[6] This is the task of the researcher, which also includes defining the relevant cut-off points in the dendrogram which is the outcome of the cluster analysis.

Previously, Canoui-Poitrine et al. have identified three groups through latent class analysis without an a priori hypothesis in a cohort of 618 HS patients, by including ten variables chosen by the researchers (three body locations, five lesion types, association with acne, and family history of HS).[12] Latent class analysis is also a statistical method to find homogenous groups/subtypes of patients in a multivariate categorical and/or continuous dataset and uses a probabilistic model for clustering, whereas in cluster analysis a distance function is used to assess the similarity between cases. Although the latent class analysis seems methodically sound, the found latent classes have not been used widely (yet), possibly due to the difficulties in assigning HS patients to solely one of the classes resulting in poor inter-rater reliability scores.[24] In 2015, Van der Zee and Jemec proposed another set of possible subtypes (six types), based on their (clinical) expert opinion.[13] Frew *et al*. proposed three subtypes, after studying and combining the results of several previous publications regarding HS phenotypes including that of Canoui-Poitrine *et al*. and Van der Zee and Jemec.[15] Theut Riis *et al*. proposed that patients with a low and high BMI could represent two clinically different subtypes within the whole HS population.[14] We have also shown that BMI is an important variable to distinguish subtypes of HS, but according to our analyses it is not the only relevant variable. Notably, until now all proposed subtypes

above have not been validated. Besides these proposed subtypes, multiple explorative/descriptive reports (e.g. case reports, case series) suggest that HS can present distinctly from classic HS (with nodules, abscesses and/or sinus tracts in the body folds), such as "plaque form" HS involving purple inflamed plaques on different parts of the body with typical cribriform scarring and HS involving ectopic sites such as the nape, the latter sometimes referred to as "atypical" HS.[16–18,20]

In our analysis we decided not to focus on presence of (certain) HS symptoms (lesion types, degree of inflammation) and affected body regions, since not a single symptom or feature of HS defines a robust subtype or phenotype. Thereby, HS often displays a dynamic disease course. For example, patients can go from Hurley stage IA to IC from IIC to III in days or progress from a Hurley stage I (without sinus tracts) to a stage with sinus tracts (II and III). As seen in this study, all (refined) Hurley stages can be seen in each category, however, some refined Hurley stages seem to be more common in certain categories than in others. Hence, in this study only four variables were chosen, which are thought to be significant and constant contributors to the HS phenotype. Furthermore, these can be assessed in any patient presenting with HS. We suggest that the identified clinical categories in this study should be used complementary to the refined Hurley staging, to have an integral depiction of the entire HS patient. This can be used for research or to make individual treatment plans in daily clinical practice (e.g. a category 4 patient "HS plus ≥1 other follicular occlusion disease" presenting with Hurley stage IC for who treatment options such as systemic retinoids or biologics are reasonable).

The current study is not without limitations. One limitation might be the relatively small sample size. However, the overall study population characteristics are similar to the average HS population. Other more frequent comorbidities (e.g. metabolic syndrome, spondyloarthritis, and Crohn's disease) and specific syndromes (e.g. PASH, PAPASH) in HS were not included as variables.[6] However, the occurrence of (multiple) associated diseases can influence therapeutic approaches and outcomes.

In summary, we identified and defined five distinct clinical categories within the HS disease spectrum through cluster analysis. This categorization of HS patients seems clinically relevant, is easily applicable, and may influence treatment strategies and outcomes. Additionally, it might contribute to future genotype-phenotype correlations and enhanced understanding of de pathophysiology of HS and therefore improvement of clinical care. We recommend further investigating and testing these clinical phenotypes in a larger cohort of HS patients.

Acknowledgments

We thank all the patients with HS who are participating in the HiSURE and HiCARE cohorts.

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