Hidradenitis suppurativa

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GENERAL INTRODUCTION AND OUTLINE AND AIMS OF THIS THESIS

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GENERAL INTRODUCTION

Hidradenitis suppurativa (HS) is a common, chronic, debilitating inflammatory skin disease of the terminal hair follicle affecting mostly the intertriginous body areas.[1] Hidradenitis suppurativa is considered to be a complex and heterogeneous disease that is difficult to treat. The exact pathogenesis and aetiology of HS is still unknown. Despite HS being a common disease, the number of studies devoted to HS is still limited compared to other common skin diseases. Fortunately, HS is losing its status as an orphan disease. In the last two decades, scientific as well as public interest in HS is increasing; more than half of all publications in HS research appeared in the past five years.

A disease without a proper name, alias hidradenitis suppurativa

About 180 years ago (1839), HS was first described by Velpeau.[2] He reported a case of a patient with abscesses in the axillary, mammary, and perianal regions, but did not give HS its current name yet. In 1854, a French surgeon called Verneuil described HS as an apocrinitis, and designated it 'hidrosadénite phlegmoneuse'.[3] This is also why HS is sometimes referred to as 'Verneuil's disease'. He proposed that inflammation of the sweat glands was the first important step in the pathogenesis of HS. In 1892, the term 'hidradenitis destruens suppurativa' was suggested by Pollitzer.[4] In 1939, Brunsting hypothesized that the apocrine, and to a lesser extent the eccrine, sweat glands where the focus of HS.[5] In 1952, Brunsting also reported commonalities of HS to acne vulgaris.[6] Scientific evidence for inflammation of the apocrine sweat glands in HS was provided first by Shelly and Cahn, and they suggested that this was caused by an infection by normal microflora from the axilla due to a hyperkeratotic obstructing plug in the apocrine duct.[7] In 1956, HS was first named 'hidradenitis suppurativa' by Pillsbury, who described HS as part of the 'follicular occlusion triad' together with acne conglobata and dissecting cellulitis of the scalp, and hypothesized that all three diseases were caused by occlusion of the hair follicle by follicular hyperkeratinisation and secondary bacterial infection.[8] In 1975, Plewig and Kligman added sinus pilonidalis to the triad, resulting in the 'follicular occlusion tetrad'.[9] In 1989, Plewig and Steger proposed to rename HS into 'acne inversa', due to the resemblance to acne and the preferred body sites of disease presentation.[10] Some still refer to HS as acne inversa, although HS seems to have a significantly different pathogenesis than acne. In some (mostly Dutch) literature, HS is referred to as 'acne ectopica'.[11] Recently, in 2017, Chen and Plewig proposed to change the name HS to 'dissecting terminal hair folliculitis', based on current histopathological knowledge of HS.[12] Although HS appears to be a misnomer, this is still the most frequently used term in clinical and scientific practice to describe the disease.

Epidemiology

Hidradenitis suppurativa is thought to be a common disease. However, the true prevalence of HS is unknown. Reported prevalence varies between 0.053% and 4.1%.[13–19] These contradictory differences are due to the different methodologies used, and might be geographically determined. The most frequently used methods determining HS diagnosis are: use of pre-existing registries, physical examination, and patient self-reported diagnosis in certain groups/populations. These different methodologies all have strengths and weaknesses. The lowest prevalence estimate was found in a North American study that used billing codes data from insurance databases.[15] The highest prevalence rate of 4.1% was found in a Danish study using physical examination as a diagnostic tool in a population that was screened for sexually transmitted diseases.[13] Few studies performed in the United States suggest that HS is more common among patients of African-American descent compared to Caucasians.[20] The average, widely accepted, prevalence of HS is often set at 1%, but remains an estimate. Females are said to be affected more often than males (about 3:1).[1]

Clinical signs and symptoms

The two core elements of HS are inflammatory nodules and sinus tracts (subcutaneous tunnel formations).[1,21] Other frequently seen lesions are abscesses, bridged scars, and post-inflammatory "tombstone" double-ended pseudocomedones.[21] Hidradenitis suppurativa typically starts after puberty with deep seated painful nodules that can progress to abscesses, and usually heal with scars. In a later stage, sinus tracts can develop. However, sinus tracts may develop rapidly after onset of HS and can even be the first noticeable symptoms, or will never develop at all. The preferred body areas for HS are the body folds: axillae, groin, gluteal, inter- and inframammary regions.[1,21] Hidradenitis suppurativa can also occur ectopically at other body sites where terminal hair follicles are present, such as the abdomen, face and neck. Hidradenitis suppurativa is known to have a chronic course with relapses and remissions. During an active disease phase inflammation is the main problem, causing symptoms such as pain and also pruritus is reported.[1,21,22] Pus can drain from abscesses and sinus tracts, often leading to an unpleasant smell and increasing discomfort for the patient. Due to the destructive nature of the disease, architectural loss at the involved body sites can occur. Additionally, patients describe symptoms of systemic malaise during flares.[23]

Diagnosis

Hidradenitis suppurativa has a clear, distinct clinical presentation. Hidradenitis suppurativa is a clinical diagnosis and there is no pathognomonic test. However, average

time for confirming the diagnosis can take up to seven years (patient's and doctor's delay).[24,25] The diagnosis of HS is made on the basis of the following three criteria according to the modified Dessau definition[21,26,27]:

1. Typical lesions: deep seated painful nodules, either suppurative or not. Other lesions frequently described are: abscesses, bridged scars, (draining) sinuses, and pseudocomedones.
2. Typical body sites: occurrence in one or more predilected areas: axillae, submammary, intermammary, inguinal areas, perineal region or buttocks.
3. Chronicity and recurrences: two recurrences in six months has (arbitrarily) been used as a diagnostic criterion. The diagnostic delay may therefore not be longer than six months.

Self-reported diagnosis of HS, based on questions comprising these three criteria, has a high sensitivity (90-97%) and specificity (82-97%). These questions were tested in cohorts of patients known with a clinical diagnosis of HS.[28,29] This makes epidemiologic research regarding HS diagnosis based on patient questionnaires feasible.

The differential diagnosis of HS includes common folliculitis, common abscess, carbuncles and furunculosis, infected Bartholin's gland, infected or inflamed epidermal cysts, lymphogranuloma venereum, scrofuloderma, actinomycosis, developmental fistulae, nodular acne and pilonidal cyst, and cutaneous presentation of Crohn's disease.[30]

Frequently, HS is staged with the use of the Hurley classification (Table 1).[31] However, the Hurley classification cannot be used to globally stage HS in a patient and determine disease severity. Importantly, the Hurley classification was designed to describe HS lesions at one affected body region and also to guide surgical treatment options. Therefore, a classification system to validly and accurately stage HS patients globally is needed in daily clinical practise and research.

Several HS severity instruments have been developed in the past years, such as the International HS Severity Scoring System (IHS4), Modified Sartorius Score (MSS), HS Clinical Response (HiSCR), Acne Inversa Severity Index (AISI), and the HS Severity Index (HSSI). Until now, none of these instruments can be used as the universal standard to globally assess HS disease severity since validation is often incomplete and/or of limited methodological quality.[32]

Table 1. Hurley classification for hidradenitis suppurativa[31]

Hurley stage	Description
I	Abscess formation, single or multiple without sinus tracts and scarring
II	Recurrent abscesses with sinus tracts and scarring. Single or multiple widely separated lesions
III	Diffuse or almost diffuse involvement or multiple interconnected tracts and abscess throughout an entire area

Aetiology and pathophysiology

Hitherto, the aetiology and pathophysiology of HS is still poorly understood. The exact chronology of pathogenic events in HS is uncertain. Currently, one of the most plausible hypotheses is that HS is an (auto-)inflammatory disease that occurs in a genetically susceptible individual exposed to certain environmental risk factors.[33–37] Follicular occlusion is assumed to be one of the first or even the central event in the pathogenesis of HS and an underlying aberrant immune system is suggested to play a key role.[38] The cause of occlusion in combination with an underlying aberrant inflammatory state is probably multifactorial. Tobacco smoking and obesity are epidemiologically highly linked to HS. Furthermore, bacteria, endocrine/metabolic alterations, and mechanical stress have been proposed to contribute to development or worsening of HS.[38]

Genetics

A family history of HS is reported by approximately one-third of patients. The pattern of inheritance suggests an autosomal dominant trait.[39–41] However, environmental factors that prevail within families such as dietary and smoking habits should not be ruled out. Linkage of HS to chromosome 1p21.1 – 1q25.3 was found in a study including a large Han Chinese family of four generations with autosomal dominant HS inheritance.[42] Heterozygous ϒ-secretase gene mutations in HS have been found, although only in a minority of HS patients, and carriage does not necessarily lead to the HS phenotype.[43–45] Mutations in either PSENEN, NCSTN or PSEN1 genes were found in a study including six Han Chinese families with autosomal dominant HS inheritance pattern. PSENEN, NCSTN and PSEN1 encodes subunits of the ϒ-secretase protease.[46] ϒ-secretase is a protease, composed of four protein subunits including nicastrin, and is involved in the Notch signalling pathway. In mouse models, ϒ-secretase deficiency leads to epidermal cysts and absence of sebaceous glands.[47] Nicastrin-deficient mice showed follicular and cystic hyperkeratosis, especially in sebaceous gland-bearing areas of the skin.[48]

Histological findings

It is known that the first structural changes in HS occur in the hair follicle, or better described as the folliculopilosebaceous unit (FPSU) (Figure 1).[49,50] Histological findings in early HS lesions are: orthohyperkeratosis of the infundibular epidermis, hyperplasia of follicular epithelium, psoriatiform hyperplasia of the interfollicular epidermis, and perifolliculitis with a lymphocytic mixed infiltrate (infundibulitis). Subsequently, the hair follicle ruptures, releasing interfollicular debris and elements (corneocytes, hair shaft fragments/keratin, and bacteria) into the dermis, triggering a neutrophilic foreign body inflammatory response. In a later stage sinus tracts can be formed (can also occur rapidly

after disease onset). The instigating pathomechanism causing follicular occlusion is still controversial.

Other histological findings are a reduced number of sebaceous glands in clinically unaffected skin in HS and an absence of periodic acid-Schiff positivity of the basement membrane zone at the sebofollicular junction in clinically unaffected skin.[51,52] The latter is hypothesized to contribute to fragility of the sebofollicular junction, however contradictory results have been found.[53] Also, an increased expression of cytokeratine 16 in interfollicular and infundibular epidermis in lesional HS skin has been reported.[54]

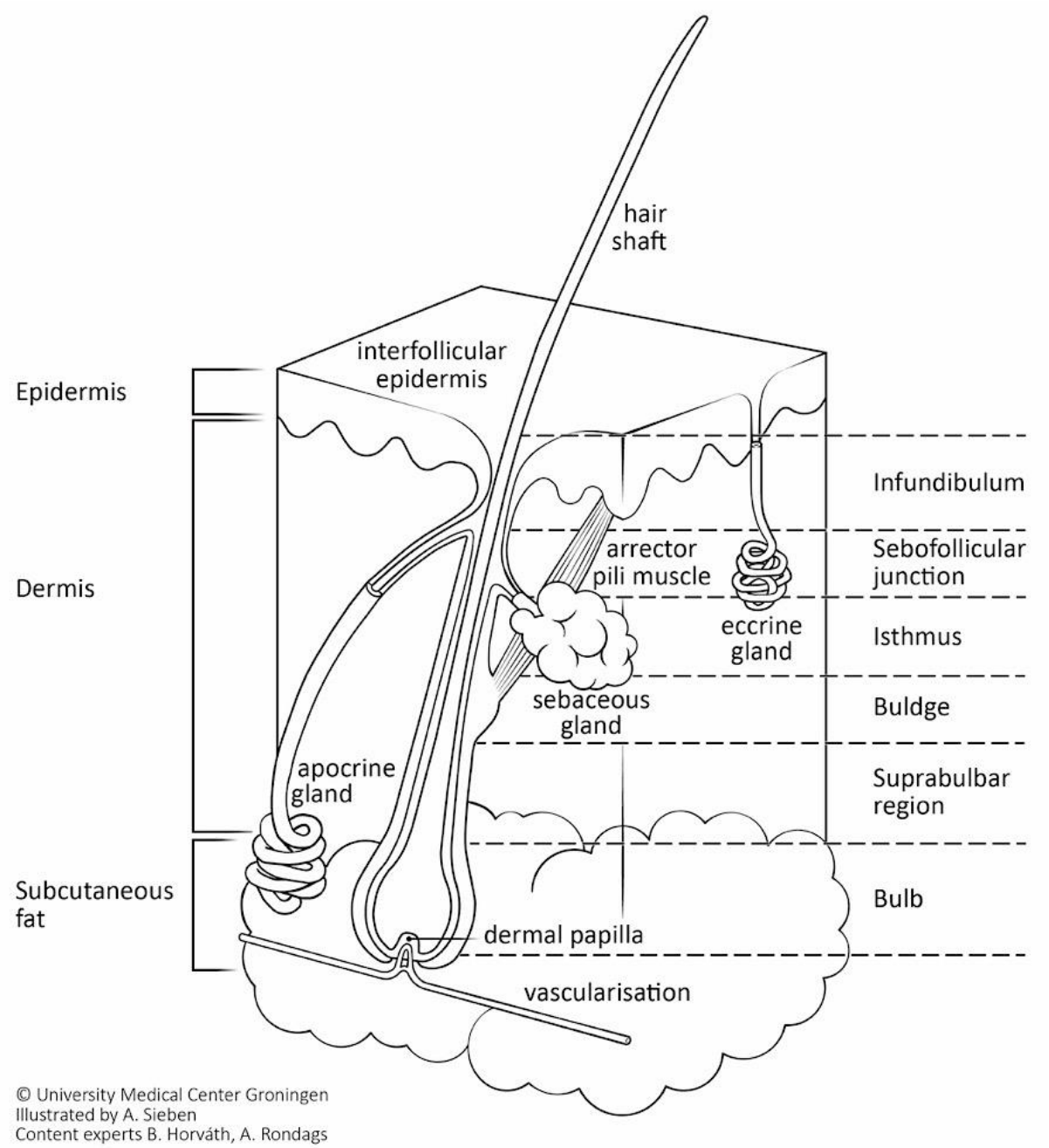

Figure 1. Folliculopilosebaceous unit

Pathophysiology of inflammation

As mentioned earlier, the exact inflammatory pathophysiology of HS is unclear.[35] Auto-inflammation, also termed innate immune-mediated inflammation, is suggested to play a key role in the pathophysiology of HS. A perturbed innate immunity is thought to contribute to HS disease; abnormal levels of innate immune effectors such as antimicrobial peptides (AMPs), complement proteins, and cytokines have been found.

Cutaneous AMPs are expressed by keratinocytes and have a role in the defence against cutaneous infections. Several studies showed aberrant increased and decreased levels of AMPs in HS skin.[55,56] Local decrease of AMPs is suggested to support the susceptibility to secondary infections.[56]

Recently, the complement system, a principal part of the innate immune system providing a host defence against various pathogenic microbes, is suggested to have a role in HS.[57–60] This system also has regulating abilities in inflammatory and immune responses.[59] Commensal follicular skin microbes could function as pathogen-associated molecular patterns (PAMPs) and cellular fragments after follicular rupture as danger (or damage)-associated molecular patterns (DAMPs), which can both activate the complement system.

A systematic review recently integrated the data about cytokine profiles in HS in different compartments: skin serum, blood or wound exudate.[36] The cytokines interleukin (IL)-1β, IL-6, IL-8, IL-17A, and tumor necrosis factor (TNF)-α were analysed by five or more studies. Of these cytokines, IL-17A seemed to have the strongest and most significant role.[36]

Tumor necrosis factor-α, a pro-inflammatory cytokine produced by innate and adaptive immune cells including T helper (Th) cells, seems to have an important role in HS, which is also demonstrated by the favourable treatment effects of TNF-α inhibitors.[21] IL-1β, a potent pro-inflammatory cytokine of the innate immune response produced by a subset of CD14+ dermal dendritic cells is reported to be relevant in HS disease by several studies.[36,61] Interleukin-1β is among IL-6, transforming growth factor β, and IL-23 one of the cytokines that drives the differentiation of Th cells.[62] Interleukin-17A, also a pro-inflammatory cytokine, is produced by Th17 cells in response to stimulation by IL-23. Interleukin-17A is also reported to be produced by innate lymphoid cells, gamma-delta T cells, mast cells and neutrophils. Enhanced expression of IL-23 by macrophages in HS was found.[55] Based on these findings it is suggested that the IL-1β-IL-23/Th17/IL-17 pathway is important in the pathogenesis of HS.[35]

Messenger-RNA microarray studies support aberrant inflammatory responses in HS.[57,60] Significant differences in gene expression in lesional skin compared to healthy skin of HS patients were found.[57] Pathway analyses of the modulated genes were mostly related to inflammation, including cell adhesion, diapedesis and extravasation as well as immune cell signalling and communication pathways. Further in depth analysis showed abundant

immunoglobulin transcripts, AMPs, an interferon signature, and plasma cells in HS skin lesions. Dysregulation of the complement system in HS blood and skin was also found.[57,60] Messenger-RNA microarray analysis of whole blood of HS patients versus healthy controls did not show significant differences.[57] Despite all these data, there is no specific biomarker found in HS yet.

Other laboratory findings suggesting systemic inflammation are elevated levels of e.g. C-reactive protein, erythrocyte sedimentation rate, neutrophils, monocytes, and serum amyloid A.[61,63]

Microbiology

Currently, HS is not considered to be a primarily infectious disease because bacterial cultures from early lesions show mainly negative results.[1] However, the intertriginous body areas where HS lesions preferably occur, are favourable for bacterial growth due to the high humidity level, presence of sebaceous glands, sweat, and (terminal) hair follicles which might suggest a possible (secondary) role for bacteria in HS.[1]

Several studies have isolated bacteria like coagulase-negative staphylococci (such as Staphylococcus epidermidis) and Staphylococcus aureus from (active and/or acute) HS lesions.[64–66] Even though these bacteria are known as part of the commensal skin flora, they are also able to cause severe infections in immunocompromised patients.[67] Interestingly, the cutaneous microbiome of HS was found to be significantly different from healthy controls in both lesional and nonlesional skin recently.[68] In lesional skin, Coryne bacterium species and Porphyromonas and Peptoniphilis species were found to be the predominant microbiome types. In nonlesional HS skin, a significantly increased diversity of the microbiota compared to HS skin and healthy controls was found, which might indicate an altered/imbalanced microbiome preceding development of HS lesions. Furthermore, Propionibacterium was found significantly less in HS skin than in healthy controls.[68]

Although antibiotics are often prescribed for HS, not all are effective, making the role of bacteria in the pathogenesis of HS still questionable. It is thought that the antibiotics that are (partially) effective in HS are those with anti-inflammatory and immunomodulatory properties, such as tetracyclines and clindamycin-rifampicin. They are usually prescribed for a period of ≥10 weeks.[1]

Endocrinology

There are several facts pointing out the importance of hormonal influences on HS. First, HS is the disease of young adults; it occurs predominantly (shortly) after puberty and onset of HS in elderly is highly uncommon.[69] Hidradenitis suppurativa affects much more females than males. These data suggest the role of sex hormones. Endocrine diseases like

polycystic ovarian syndrome, diabetes, and thyroid disease are reported to be more common in HS patients than in controls.[16,38] Therefore, endocrine factors are suggested to play a role in HS, however, the exact mechanism in HS remains unclear. Contradictory results have been reported regarding the effect of male and female sex hormones on HS. The majority of HS patients exhibit normal androgen levels. However, HS frequently improves during pregnancy and during the use of (oral) contraceptives when oestrogen levels are high, and worsens postpartum and just before menstruation when oestrogen levels decrease. Onset of HS after menopause is uncommon. It has been proposed that hormones execute a focal hormonal dysregulation, i.e. at the site of the FPSU, however this still needs to be investigated.[69,70]

Risk factors

Besides a genetic predisposition, two major identified risk factors for HS are obesity and smoking. Most HS patients are overweight or obese.[71] Adiposity leads to a low-grade pro-inflammatory state systemically, which may contribute to inflammatory reactions in HS. Additionally, obesity also leads to increased skin-skin contact, friction, and follicular microtrauma.[72] It is hypothesized is that mechanical stress or friction induces hyperkeratosis.[72] Nicotine and tobacco smoke components are thought to influence HS by for instance promoting epidermal hyperplasia and keratinization leading to infundibular occlusion, altering the skin immune response, increasing pathogenic effects of microbes and decreasing skin AMPs.[35] Other risk factors mentioned to maintain or aggravate HS are stress, heat, exercise, sweating, tight clothing, deodorants, and shaving, although reports are limited.[38,73]

Integrated pathophysiological theories

One proposed integrated pathophysiological hypothesis is that in a genetically susceptible individual that is exposed to environmental factors, an underlying aberrant inflammatory state exists.[35] Certain events, such as an aberrant AMP production and deficient Notch signalling, contribute to intra-follicular changes: epidermal hyperplasia and infundibular keratosis with subsequent follicular occlusion and cyst formation. Subsequently, follicular rupture causes expulsion of free keratin, corneocytes, hair shaft fragments, sebum, and commensal bacteria in the dermis. These act as DAMPs and PAMPs, and are thus recognised by the immune system as foreign bodies. This activates the NLRP3 inflammasome with caspase-1 mediated cleavage of pro-IL-1β into IL-1β leading to pro-inflammatory effects.[33,35] Inflammation is maintained by various immune cells, such as T cells (mainly CD4+, but also CD8+), B lymphocytes, macrophages and neutrophils, and their products such as IL-17, TNF-α, and IL-23.[35]

Another hypothesis suggests an imbalance (i.e. increase) in the ratio of Th17 and T regulator (Treg) cells in lesional HS skin, leading to an impairment of the follicular stem cells' homeostasis. This is presumed to affect the integrity of the infundibulum of terminal hair follicles, leading to dissection and subsequently perifollicular inflammation.[12,74,75] Whether these disturbances occur primarily or secondarily is unknown. Smoking, obesity and decreased Notch signalling also seem to contribute negatively to the Th17/Treg ratio.[75] One publication reported that all drugs with beneficial effects in HS have normalizing effects on the Th17/Treg ratio.[75]

Interestingly, abnormal levels of TNF-α, IL-17A, IL-1β, and IL-23 and imbalanced Th17/Treg ratio were also reported for HS associated auto-inflammatory diseases, such as spondyloarthritis (SpA) and inflammatory bowel disease (IBD).[75–78] Many findings support the hypothesis that HS may be a systemic disease.

Comorbidities

Hidradenitis suppurativa is associated with a range of co-morbidities including auto-inflammatory diseases such as IBD, SpA, pyoderma gangrenosum (PG), the metabolic syndrome, the follicular occlusion tetrad, and acne. Furthermore, HS is associated with a significant psychosocial morbidity. The findings of these associations have contributed to the understanding of the pathophysiology of HS and the hypothesis of HS being a systemic (auto-)inflammatory disease. It is important to recognize and identify symptoms of co-morbidities as these can influence treatment choices and outcomes.

<u>Auto-inflammatory diseases</u>

Multiple publications report an association between HS and IBD. Questionnaire based studies found an HS prevalence of 6.8-10.6% to as high as 23% in IBD patients, especially in patients with Crohn's disease.[79–81] An electronic health record database study performed in the United States identified that Crohn's disease was significantly more prevalent in HS patients than in patients without HS (2.0 vs. 0.6%).[82] Another cross-sectional study from Israel also found a significant association between HS and Crohn's disease, but not for ulcerative colitis.[83] In a Danish study, using nationwide registers, Crohn's disease and ulcerative colitis were both more prevalent in patients with HS than in the general population (Crohn's disease 0.8% vs. 0.3% and ulcerative colitis 1.3% vs. 0.7%).[84] HS and IBD, particularly Crohn's disease, share similarities. Similar to HS, cutaneous presentation of Crohn's disease can present with sterile abscesses and sinus tracts in the perineal and inguinal areas and both are associated with arthritis. An aberrant immune response is thought to play an important role in both of these chronic inflammatory diseases.[85] Cutaneous Crohn's disease can be mistaken for HS and vice versa.[86] In contrary to Crohn's disease, HS does not form rectal fistulas. Sometimes it is necessary to perform a magnetic

resonance image to distinguish between both diseases.[87] Furthermore, both diseases respond well to anti-inflammatory therapy with TNF-α inhibitors.[21,88]

Hidradenitis suppurativa is also reported to be associated with SpA, previously known as seronegative spondyloarthritides. Spondyloarthritis is a heterogeneous group of interrelated chronic inflammatory articular rheumatic conditions, which include ankylosing spondylitis (AS), psoriatic arthritis, arthritis related to IBD, reactive arthritis, and undifferentiated SpA. These conditions share clinical symptoms and are associated with the HLA-B27 gene. Two recent publications showed a higher prevalence of SpA in the HS population than in the general population (±1%), but the reported prevalence rates have a wide range of 2.3%-28.2%.[89–93] However, it is not known what the prevalence of HS in SpA is. Interestingly, commonalities between HS and SpA include the association with IBD and the shared treatment option of TNF-α inhibitors.[21,92]

Hidradenitis suppurativa is also associated with PG, an inflammatory (neutrophilic) dermatosis. Pyoderma gangrenosum is also associated with IBD and rheumatoid arthritis, psoriatic arthritis, AS, and inflammatory arthritis.[94] Several syndromes have been described with HS and PG: PASH (PG, acne conglobata, and HS), PAPASH (pyogenic arthritis, PG, acne, and HS), and PsAPASH (psoriatic arthritis, PG, acne, and HS). In PASH and PAPASH, underlying genetic mutations that lead to an increased IL-1β mediated inflammation have been described.[95]

Metabolic syndrome

Metabolic factors are suggested to play a role in HS. Metabolic syndrome criteria, hypertriglyceridemia, central obesity, reduced levels of high-density lipoprotein cholesterol, and hyperglycaemia, were all found to be more prevalent in HS patients than in controls.[96–98] About one third to half of HS patients appear to suffer from metabolic syndrome, and this is significantly more than the control population.[96–98] It is suggested that a high systemic burden, which may occur in severe HS, leads to insulin resistance. Also, lifestyle aspects (overeating, lack of exercise) may contribute to development of metabolic syndrome and therefore indirectly to the development of HS. Metformin as therapeutic option in refractory HS disease has shown effectiveness in HS, which further supports the association between HS and metabolic disorders.[99,100]

Follicular occlusion tetrad and acne

Similar to HS, follicular occlusion is also an etiologic event in acne conglobata and dissecting cellulitis of the scalp. In 1951, these three diseases were described as the follicular occlusion triad and in 1975 another disease with follicular occlusion was added to this triad, namely pilonidal sinus, forming the 'follicular occlusion tetrad'.[9,101] Acne vulgaris

has also been epidemiologically associated with HS; about a fourth to one third of HS patients have or have had acne.[102,103]

Other physical co-morbidities and complications

Other somatic co-morbidities or complications suggested to occur more frequently in HS patients than in controls without HS include anaemia, kidney disease, and squamous cell carcinoma in patients with long standing HS.[38,104] Also, congenital disorders such as Down syndrome, Dowling Degos, and keratitis-ichthyosis-deafness syndrome have been reported to co-occur with HS.[105–108]

Psychological comorbidities and burden

Hidradenitis suppurativa is known to be a debilitating skin disease, impairing the patient's quality of life (QoL) significantly on a private and professional level.[109,110] Symptoms of pain, suppuration, unpleasant smell, pruritus, and involved body locations contribute profoundly to the HS patient's diminished wellbeing.[110] Compared to other skin diseases, patients with HS score among the worst on QoL measurements.[29,111,112] A higher incidence of depression and anxiety was found in HS patients compared to controls.[113] Up to 39% of HS patients have been reported to suffer from depression. Similar inflammatory pathomechanisms between HS and depression has been suggested, indicating not only subjective feelings increase the risk of depression in HS.[75] Suicide risk is also said to be increased.[114] Furthermore, the sexual health of HS patients is reported to be significantly impaired, especially in females and females with late onset HS.[115]

Treatment

Hidradenitis suppurativa is a heterogeneous disease, for which still no phenotypes are defined and validated. Therefore, tailored treatment of HS can be challenging and there is no cure. This is largely due to the facts that the pathogenesis of HS is not fully understood; the primary event is not eliminable and a large number of (high-quality) randomized, control trials are still missing. Moreover, it is difficult to compare different studies due to variations in methodology/outcome parameters, as core outcomes are not defined yet.[116] However, there is an on-going project to achieve consensus about the core outcomes in HS (HIdradenitis SuppuraTiva cORe outcomes set International Collaboration, HISTORIC).[117,118] Therapeutic options thus far includes patients' education about the disease itself, life style interventions, medical and surgical interventions and pain management (Table 2). Often, a holistic, multimodal, treatment approach combining anti-inflammatory and surgical treatment is recommended and due to its chronicity long-term maintenance treatment is necessary. The main objectives are to gain rapid control of

Table 2. Standard treatment options for hidradenitis suppurativa

Education	About disease pathophysiology, chronic recurrent character, treatment options, and treatment goals
Lifestyle intervention	Smoking cessation
	Weight reduction
	Avoid trigger factors known to patient
Topical treatment	Resorcinol 15% cream once daily
	Clindamycin 1% lotion
	Anti-bacterial soap
Medical treatment	Tetracyclines
	Clindamycin-rifampicin
	Rifampicin-moxifloxacin-metronidazole
	TNF-α-inhibitors (adalimumab)
	Acitretin
Surgery	Deroofing
	Limited excision (skin-tissue-saving excision with electrosurgical peeling)
	Wide excision
Acute flares	Incision and drainage
	Intralesional, topical or (short duration) systemic corticosteroids
	Resorcinol 15% cream twice daily
Pain management	Acetaminophen
	Nonsteroidal anti-inflammatory drugs
	Opiates
	Anticonvulsants
	Selective serotonin reuptake inhibitors / serotonin-norepinephrine reuptake

inflammation and relieve symptoms, prevent relapses, prevent tissue damage, prevent superinfection, achieve long-term disease remission, and to improve QoL.[21]

Education and lifestyle interventions

Because HS is difficult to treat and to prevent disappointment and frustration, a cornerstone of treatment of HS is educating the patient about HS disease, treatment, and treatment goals.

Life style interventions such as cessation of smoking and weight loss should be recommended and guided. Unfortunately, scientific evidence is still lacking to support the effectiveness of life style interventions in HS.[21]

Topical treatment

Medical options for HS can be divided into topical and systemic treatment. Topical treatment is suitable for mild HS, such as the keratolytic resorcinol 15% cream with anti-inflammatory and itch reducing properties and topical clindamycin 1% that has anti-inflammatory and anti-septic properties. Antibacterial soap can be prescribed as maintenance therapy to prevent secondary bacterial involvement, however evidence

regarding topical antiseptic treatments are lacking.[21] Specific wound care (foam) dressings to prevent leakage can contribute to the comfort of the patient.

Systemic treatment

Systemic treatment is indicated in moderate to severe inflammatory HS. Antibiotics with anti-inflammatory properties like tetracyclines are frequently prescribed, and if this is ineffective, combination therapy of clindamycin and rifampicin or rifampicin, moxifloxacin, and metronidazole can be given. In more severe and recalcitrant inflammatory HS, TNF-α inhibitors (biologics) are indicated. Currently, adalimumab is the only biologic approved for HS.[21] Acitretin, a systemic retinoid, can be prescribed in men and non-reproductive women, and seems most suitable in migratory nodules and abscesses and presences of evident follicular plugging (pseudocomedones). It inhibits excessive cell growth and keratinisation.[70,119]

Surgery

Surgery is indicated for recurrent or persistent/chronic HS lesions. More permanent lesions can be treated with deroofing or limited excision, with 'skin-tissue-saving excision with electrosurgical peeling' (STEEP) or wide excision techniques.[21,120,121] However, there is no consensus about surgical definitions and outcomes in HS.

Acute exacerbations

An acute abscess can be treated with incision and drainage to relieve pain.[21,120] Acute exacerbations can be managed with intralesional, topical or (short duration) systemic corticosteroids.[21,122] Also, topical resorcinol 15% twice daily can be recommended.[123,124]

Pain management

Adequate pain control is mandatory in HS, as pain is one of the main symptoms in HS. Although anti-inflammatory medicines and surgery can reduce pain, adjuvant pain medication is often required.[125] General pain guidelines (such as the World Health Organisation pain ladder) can be followed. First-line options are topical analgesics, oral acetaminophen, and oral nonsteroidal anti-inflammatory drugs. When these are insufficient, oral opiates can be necessary. Furthermore, anticonvulsants and selective serotonin reuptake inhibitors / serotonin-norepinephrine reuptake inhibitors can alleviate HS associated neuropathic pain, as well as reduce feelings of itch and depression.[125]

Other options

Other treatment modalities, such as dapsone, ciclosporin A, antiandrogens, metformin, laser therapy, and zinc gluconate have been investigated, although studies are sparse.[21]

Dapsone has antibacterial and anti-inflammatory properties and ciclosporin A immunosuppressive activity.[21] Both therapies should only be considered when HS is refractory to standard treatment. Antiandrogens such as cyproterone acetate-ethinyl estradiol should be considered in women with evident pre-menstrual flares or irregular menses and clinical or aberrant blood hormone levels suggesting hyperandrogenism.[21] Metformin is suggested to be beneficial in (refractory) HS, by reducing hyperandrogenism through reducing ovarian overproduction of androgens.[99,100] Laser therapy, like Nd:YAG, alexandrite, diode, and intense pulsed light laser, aiming to reduce the number of hair follicles in HS areas are suggested to improve HS after treatment, although long-term follow up is lacking.[126] Zinc gluconate might be effective in HS, by inducing an alteration of innate immunity in HS skin.[127]

Disease course and prognosis

There is limited data about the prognosis of HS. A questionnaire based study reported that the average duration of a boil was 6.9 days and HS patients reached their maximum disease activity after a mean disease duration of 6.4 years.[73] However, disease severity was not specified. One cross-sectional study with a mean follow-up time of 22 years found a patient self-reported remission of HS of 39% (defined as no inflammatory boils within the last six months), improvement by 32%, unchanged severity by 21%, and worsening by 9%.[128] Tobacco smoking and obesity were more common in the group without remission, suggesting lifestyle factors play a role in the prognosis of HS.[128] A retrospective patient questionnaire based study found that patients with Hurley stage III had a quicker and more aggressive disease course compared with patients with Hurley stage II HS.[129] This study also suggests that a relatively rapid disease progression from Hurley I to Hurley II is a predictive factor to develop Hurley III HS, and could therefore be a sign of a poor prognosis.[129]

OUTLINE AND AIMS OF THIS THESIS

In this thesis, seven studies covering four topics about hidradenitis suppurativa (HS) are presented. The first topic is about the prevalence of HS in patients with the rheumatologic disease spondyloarthritis (SpA) and vice versa (**Chapter 2 and Chapter 3**). In the second topic, the validation process of the refined Hurley classification for HS and symptom self-assessment of HS based on the refined Hurley classification are presented (**Chapter 4, Chapter 5, and Chapter 6**). A study to define patient categories in HS is presented in the third topic (**Chapter 7**) and in the last topic, mechanical stress as an exogenous risk factor for HS is discussed (**Chapter 8**). Background information on each topic is described below.

1. Hidradenitis suppurativa and spondyloarthritis

Spondyloarthritis, previously termed seronegative SpA, is an umbrella term for an interrelated group of chronic auto-inflammatory rheumatic diseases that includes ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease (IBD), and undifferentiated SpA.[92] These disease subtypes share clinical and immunological features, including inflammation of joints and entheses at peripheral and/or axial sites. Furthermore, extra-articular manifestations (EAMs) can be found in SpA such as IBD, uveitis, and psoriasis. There is absence of diagnostic autoantibodies (seronegative). Prevalence rates of SpA as a whole vary globally: from 0.2% in South East Asia to 1.6% in Northern Arctic communities.[130] In Northern Arctic communities, SpA prevalence is similar to prevalence of rheumatoid arthritis. The overall average prevalence of SpA is approximately 1%.[93] A strong association between SpA and human leukocyte antigen (HLA)-B27 (a major histocompatibility complex class I molecule) exists, which is considered to be a major genetic risk factor in SpA.[92]

Recently, the Assessment of SpondyloArthritis international Society (ASAS) developed the currently most used classification for SpA.[131–133] However, importantly, SpA is a clinical diagnosis made by a rheumatologist. The SpA patient can be classified into predominantly axial SpA or peripheral SpA, although they may have overlapping features. The ASAS classification criteria include clinical, laboratory (e.g. HLA-B27 positivity), and imaging SpA features (e.g. sacroiliitis on imaging) (Figure 2).[133]

In axial SpA, sacroiliitis and spondylitis (i.e. inflammation of the sacro-iliac (SI) joints and spine, respectively) are the hallmark of the disease. Axial SpA consist of AS (in Dutch also named Bechterew's disease) and non-radiographic axial SpA. In AS, radiographic damage of SI-joints can be detected on an X-ray of the pelvis. In non-radiographic axial SpA structural damage of the SI-joints cannot (yet) be detected on X-ray, however inflammation defined as bone marrow oedema at the SI-joints can be seen on magnetic resonance imaging with fat-suppression technique. It is assumed that non-radiographic

axial SpA is most often an early stage of AS.[92] However, not all non-radiographic axial SpA patient will develop into AS.

Patients with peripheral SpA present predominantly with arthritis, enthesitis, and/or dactylitis.[92] Peripheral SpA patients can be diagnosed as psoriatic arthritis, arthritis associated with IBD, reactive arthritis, and undifferentiated peripheral SpA.

Similar to HS, the exact pathophysiology and aetiology of SpA are not fully understood. An increasing body of evidence suggests that SpA and HS, but also IBD (one of the diseases epidemiologically linked to HS and SpA) share a similar pathogenesis. Elevated levels of tumor necrosis factor-α, interleukin (IL) 17A, IL-1β, and IL-23 are reported for HS as well as SpA and IBD, suggesting a similar aberrant immune mediated response.[76–78]

In **Chapter 2**, the prevalence of HS symptoms is investigated in patients with axial SpA from the Groningen Leeuwarden Axial Spondyloarthritis (GLAS) cohort. These patients were requested to fill in a symptom self-assessment questionnaire based on validated diagnostic questions with high sensitivity and specificity to identify HS symptoms. Conversely, in **Chapter 3**, the prevalence of self-reported axial and peripheral SpA symptoms in HS patients is studied through a symptom self-assessment questionnaire.

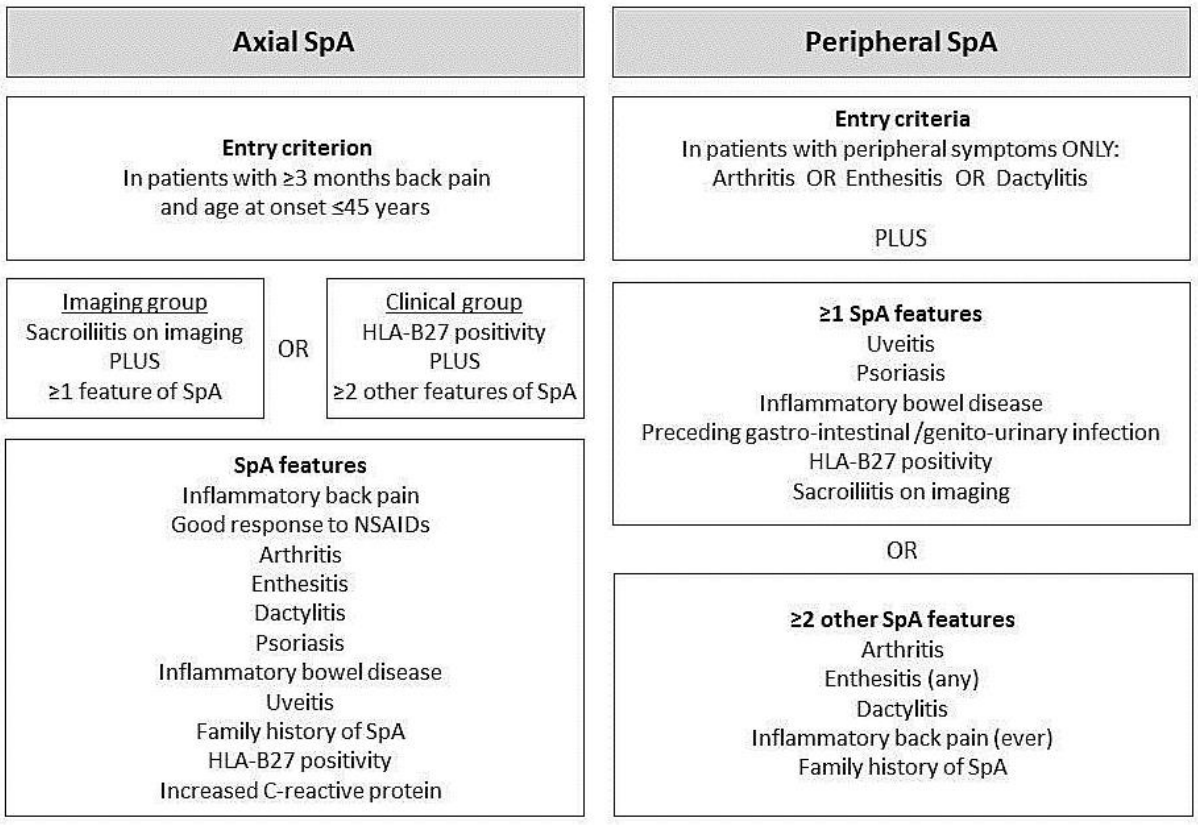

Figure 2. The Assessment of SpondyloArthritis international Society criteria for axial spondyloarthritis and peripheral spondyloarthritis[133]

SpA, spondyloarthritis; HLA, human leukocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs.

2. Refined Hurley classification for hidradenitis suppurativa

After a patient is diagnosed with HS, the patient is usually classified to indicate current disease symptoms. Originally, the Hurley classification was developed in 1989 by the dermatologist H.J. Hurley to identify HS symptoms in one body region for surgical treatment purposes (Table 1, General introduction).[31] Although simple in use, and therefore popular, the Hurley classification was not developed to stage a whole HS patient and to define disease severity (i.e. stage I being mild, II moderate, and III severe) as it does not take into account inflammatory signs and extensiveness of the disease. Furthermore, it has never been validated.[116] As such, it is not suitable to guide holistic treatment plans and does not reflect current disease activity.[134,135] Therefore, a modification of the Hurley classification was proposed recently by a Dutch panel of HS experts.[136]

When breaking HS down to its core symptoms and signs, the developers of the refined Hurley classification agreed on three main items that are important to classify the entire HS patient:

- the presence of inflammation, to guide anti-inflammatory treatments;
- the presence of operable sinus tracts, to guide surgical treatment approaches;
- the extensiveness of the disease, i.e. number and size of the involved body areas.

The refined Hurley classification contains a three-step algorithm after which the HS patient is classified into one of the seven stages (Figure 3). Hurley I and II are subdivided in three sub stages each, i.e. IA, IB, and IC and IIA, IIB, and IIC. The letters A, B, and C are suggested to represent HS disease severity, in which A stands for mild, B for moderate, and C for severe disease. Refined Hurley stage III is not sub-staged, but is redefined: at least 1% of the body surface area in an involved body area is affected with interconnected sinus tracts with the presence of inflammatory sinus tracts. Regardless of the number of affected body regions, refined Hurley stage III is always considered as severe HS disease as well.[136]

Before a new (or refined) classification can be implemented, it is important to assess its validity. However, there are no clear-cut existing guidelines on validation of classification systems in medicine. Literature about the methodology for validation of measurement systems in medicine is more substantial.[137] In this thesis, the first steps are made to investigate whether the refined Hurley classification is a sound system to classify HS patients. At a minimum, the interrater and intrarater reliability should be analysed. Due to the underlying severity scale in the refined Hurley stage I and II, these sub-scales can be regarded as (ordinal) measurements scales. Therefore, the construct validity can be investigated, which indicates the degree to which the refined Hurley severity sub-scales imply what it is measuring/indicating.

In **Chapter 4,** the construct validity of the refined Hurley classification is investigated by correlating it to the dermatology life quality index (DLQI, a patient reported quality of life measurement) and to the International HS Severity Score System (IHS4, objective disease

severity assessment), and in **Chapter 5** the interrater and intrarater reliability are assessed. Also, the face validity is explored, which is a test that indicates how well the refined Hurley classification is subjectively viewed as covering the concept it aims to measure. In **Chapter 6,** a patient self-assessment questionnaire based on the refined Hurley classification is developed and tested in a patient cohort.

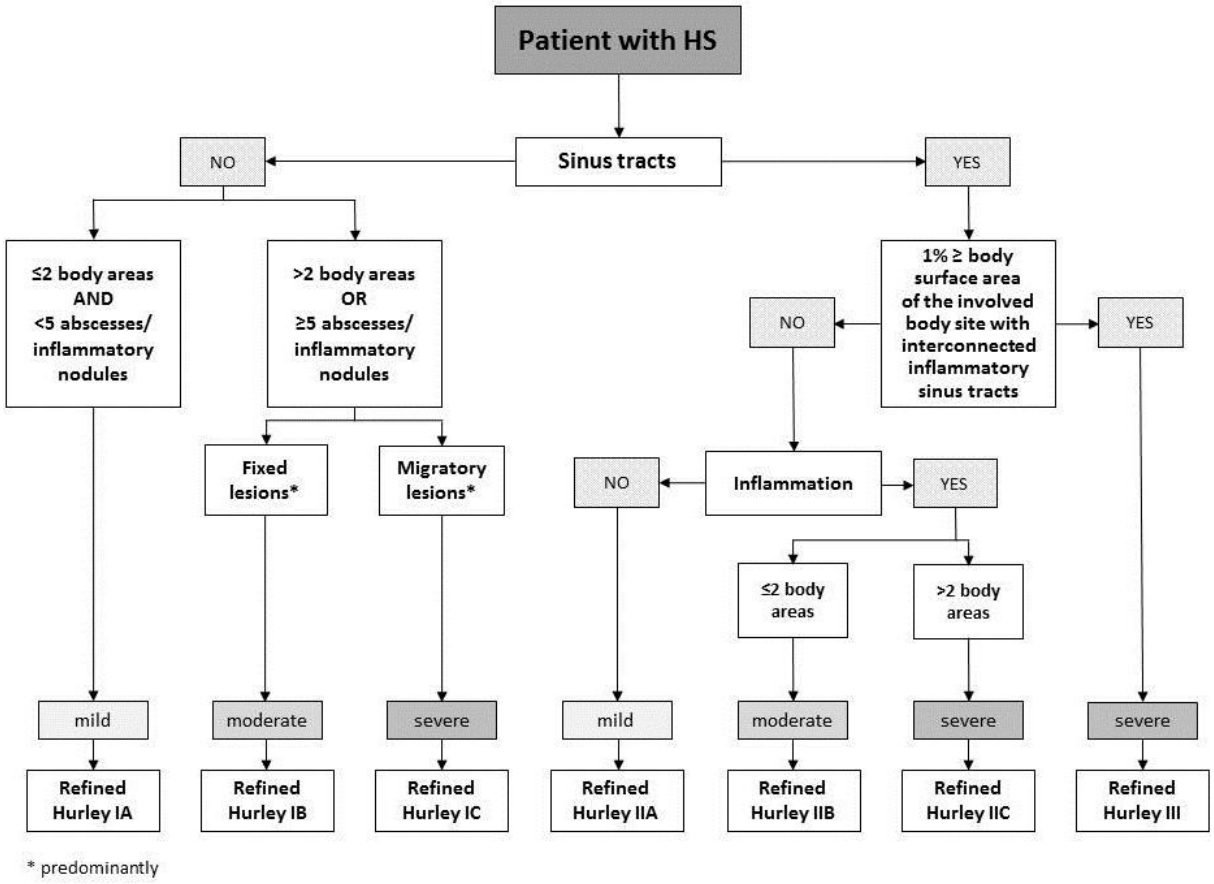

Figure 3. Refined Hurley classification flowchart[136]

3. Clinical categories of hidradenitis suppurativa

Besides heterogeneous γ-secretase gene mutations in a minority of HS patients, other possibly relevant underlying genetic mutations in HS have not been uncovered yet.[138] It is reported that HS displays a certain phenotypic heterogeneity.[138,139] Identification and accurate description of the phenotype(s) of HS patients can assist in understanding many aspects of HS disease such as aetiology, pathophysiology, and treatment, and can help to enhance phenotype-genotype correlations. So far, scientifically identified and validated clinical phenotypes for HS do not exist yet.[33,139–143] Definitions for 'clinical phenotype' vary from a single, few, multiple or the sum of all observable characteristics (disease/patient) that describes differences between individuals with a certain disease as they relate to clinically meaningful outcomes. In order to contribute to the sound description of clinical phenotypes in HS, cluster analysis was performed on a multi-centre patient cohort of adult patients with HS to identify distinct patient categories in HS in **Chapter 7.**

4. Mechanical stress as a risk factor in hidradenitis suppurativa

One of the frequently proposed risk factors for HS is the exogenous influence of mechanical stress or friction.[144] Currently, it is still unknown why HS preferably presents in the intertriginous body sites. One theory is that the body folds are more predisposed to mechanical friction or stress than non-intertriginous body areas.[144] Unfortunately, no experimental evidence exists to support the hypothesis that mechanical stress is a cause or aggravating factor of HS. In **Chapter 8,** a case is reported of a male patient known with HS and working as a road maker, who developed an ectopic HS lesion on his dorsal foot area.

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