Hidradenitis suppurativa

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Abstract
Hidradenitis suppurativa is a chronic disease characterized by recurrent, painful, deep-seated, rounded nodules and abscesses. Subsequent hypertrophic scarring and suppuration of apocrine gland bearing skin: axilla, groin, peri-anal and perineal regions are main features. Onset is usually after puberty, although it is most common during the third decade and may persist in old age. The disease tends to become chronic with subcutaneous extension leading to indurations, sinus, and fistula having a profound impact on the quality of life.
The prevalence has been estimated at 1%, but is usually considered lower. Axillary, and inguinal involvement is more common in women; perineal form in men.
The exact etiology remains unknown. The primary event is a follicular occlusion with secondary inflammation, infection and destruction of the pilo-sebaceo-apocrine apparatus and extension to the adjacent sub-cutaneous tissue. Although infection and hormonal influence are commonly observed, they are not the primary etiologic factor. Smoking may be a triggering factor. Obesity aggravates the discomfort.
Differential diagnostic includes Crohn disease, nodular acne and furonculosis. The main complications are fistulae, arthropathy, carcinoma and amyloidosis.
Treatment depends upon the stage of the disease. Early lesions are usually treated by medical therapy such as antibiotics for acute stage; long term antibiotics, systemic steroids, estrogens, anti-androgens, retinoïdes have been used as options for the chronic stage with limited success. Surgical treatment includes incision and drainage, followed by antibiotics for limited nodules, limited excisions. Total wide excision and healing with secondary intention or flaps and grafts is the only curative procedure in case of advanced disease.

Key-words
hidradenitis suppurativa; Verneuil's disease; apocrine sweat glands; *acne inversa*

Disease name	*Acne inversa*
Hidradenitis suppurativa;	
Verneuil's disease;	

Definition

Hidradenitis suppurativa (HS) is clinically characterized by recurrent, painful, deep-seated, rounded nodules and abscesses with subsequent hypertrophic scarring and suppuration of apocrine gland bearing skin. The disease tends to become chronic with subcutaneous extension leading to hypertrophic scarring, sinus, and fistula. It has a profound impact on the quality of life.

Diagnostic criteria

The diagnostic relies on the presence of:

Typical lesions i.e. deep-seated painful nodules: "blind boils" in early lesions; abscesses, fistular, bridged scars and "tombstone" open comedos in secondary lesions.

Typical topography i.e. axilla, groin, perianal region, infra mammary region.

Chronicity and recurrences

As the disease and its diagnostic criteria are frequently ignored, a lag time of several years between the first manifestation and a formal diagnostic of HS is commonly reported by patients.

Clinical description (Jemec *et al.* 2003, von der Werth *et al* 2000[a], Slade *et al* 2003, Jemec, 1988)

The onset of disease is usually after puberty and it worsens mainly during the second and third decades.

The early lesions are solitary, painful nodules that may persist for weeks or months without any change or with occasional episodes of inflammation. Early lesions are characteristic and lead to differential diagnosis from furonculosis – a frequent mistake. It includes the shape (round rather than pointed, without central necrosis) and the location which is deep. Main duration of a single painful boil is 7 days but as the average number of new nodules is two per months (range one/year - 30/month), more than half of the patients are permanently suffering from at least one lesion**.** (von der Werth *et al* 2001) The nodules may remain blind *i.e*. fail to burst, but the majority will develop into abscesses and eventually rupture externally, draining purulent material. This leads to chronic sinus formation, with intermittent release of serous, purulent, or bloodstained discharge. Ulceration sometimes occurs, and the abscesses may burrow and rupture into the neighboring structures. Multiporous or uniporous "tombstone" comedos are frequent. Healing occurs with dense fibrosis, which may appear as indurate plaques, which in axilla and groin, manifest as linear bands. Regional lymphadenopathy is characteristically absent..

The affected sites are, by order of frequency: axillary, inguinal, inner thighs, perianal and perineal, mammary and inframammary, buttocks, pubic region, scrotum, vulva, chest, scalp, retroauricular, eyelid. Axilla, groin and submammary region are most commonly affected in women; perineal and peri-anal skin tend to be more severe in males. Several sites usually symmetric may be simultaneously affected; recurrences occur in and around the original site.

Seriousness and course of the disease are variable, but untreated HS is typically a relentless progressive disease with acute exacerbations and remissions that lead to dramatic clinical picture. Pain, discomfort, swelling, malodorous discharge contribute to the burden of the disease. The quality of life is severely impaired. (von der Werth *et al* 2001)

Complications

The complications of long-standing untreated disease include:

- Fistulae formation – unusual – into the urethra, bladder, rectum, or peritoneum. (Slade *et al* 2003)
- Consequences of chronic suppuration may include anemia, hypoproteinemia, amyloidosis
- Peripheral and axial arthropathy. (Rosner *et al* 1993)
- Chronic malaise and depression
- Lymphatic obstruction and lymphoedema of the limbs, scrotal elephantiasis
- Squamous cell carcinoma may complicate perineal and buttock localizations; (Cosman *et al* 2000, Humphrey *et al* 1969 , Donsky *et al* 1964 , Gordon 1977) The risk of cancer seems to be higher for patients with HS than in control especially for lung and bucal cancers (Lapins *et al* 2001[b]). This may be explained by the high incidence of smokers affected by HS.

Associated diseases

Acne and "follicular tetrad"

Pathological studies demonstrate that the initial event in HS, like in acne, was a follicular occlusion. Association of HS with severe nodular acne – *acne conglobata*- and/or with dissecting cellulitis of the scalp has been reported. Pilonidal cysts are frequently associated with HS. Moreover comedones are frequent in both acne and HS. According to these findings some authors have proposed to rename HS as "*acne inversa*" and to include the above-mentioned diseases in an "*acne tetrad*" (Janssen *et al* 2001). However this clinical picture is not frequent. A prospective study of 70 women with HS and 100 controls failed to find any difference in the prevalence of acne, hirsutism or irregular

periods between the two groups (Jemec 1988). Contrary to the initial lesions of acne, comedones in HS are never closed; they are a secondary "tombstone comedo". Elevated sebum excretion, which is major pathophysiological feature of acne, is absent in HS. (Jemec *et al* 1997) Finally effective treatments of acne: long-term tetracyclines, Isotretinoïne and/or anti-androgens are not, or poorly effective in HS. Hence if Hidradenitis suppurativa is not a good denomination of the disease, "*acne inversa*" is not better and should be discarded until a better knowledge of the pathophysiology which may help to find a better name. In the meantime Verneuil's disease is the least ambiguous term.

Dowling Degos' disease

Reticulate pigmentation of the flexures may be sometimes associated with HS. (Balus *et al* 1993, Fenske *et al* 1991)

Crohn's disease

It's both a differential diagnostic and an associated disease. Cutaneous Crohn disease must be differentiated from HS in its peri-anal localization and the clinician should always take in his mind the possibility of Crohn disease mimicking HS in case of peri-anal lesions and eventually perform the necessary investigations. (Church *et al* 1993). The presence of discrete epithelioïd granulomas in the dermis away from the site of active inflammation may alert; (Attanoos *et al* 1993) but biopsies are not frequently performed in patients with HS. True association does exist including cases of axillary HS. Several case reports and few series of this association have been reported. They demonstrate the efficacy of infiximab on both diseases. (Adams *et al* 2003, Katsanos 2002, Martinez *et al* 2001, Sullivan *et al* 2003, Harrison *et al* 1985)

Differential diagnosis

Carbuncles and Furonculosis (Slade *et al* 2003, Jemec *et al* 2003**)** is the main difficulty when dealing with early lesions
Infected Bartholin's gland
Infected or non-inflamed epidermal cysts (improperly called steatocystoma multiplex)
Lymphogranuloma venereum , Scrofuloderma, Actinomyces
Developmental fistulae
Nodular acne and pilonidal cyst which may be associated
Crohn disease

Etiology

Morphology

HS was initially described as a disease of the apocrine gland; histologic studies reveals that the earliest lesion was a follicular occlusion and that inflammation and necrosis of the sebaceous and apocrine gland was a secondary phenomenon (Jemec *et al*, 1996[a]). Sinus track formation is a hallmark of the disease. (Janssen *et al* 2001) An echographic study of hair follicles of healthy skin of HS patients highlighted their wide diameter and distorted shape and their deep location contrarily to what is observed in acne. (Jemec *et al* 1997 [a]). These structural abnormalities could explain the specific findings of HS and may be a clue to determine the genetic factors.

Genetic factors

.A family history is given by 30-40 % of patients (Jemec *et al* 1988). However specific genetic studies yielded to conflicting results (Von der Werth *et al* 2000[b]). HLA association is not significant (Lapins *et al*, 2001[a]). An autosomal dominant pattern has been reported in several families but with variable penetrance. (Fitzsimmons *et al* 1984).

Infection

Traditionally, Bacteria are implicated in HS. Streptococci, staphylococci, and Escherichia coli are found in the early stages of the disease. During the chronic relapsing stages, anaerobic bacteria and Proteus species are more commonly present. The infectious process, always present, sometimes responsible for acute complications *i.e.* cellulitis, plays an important role in most overt clinical manifestations, but is not the initial causative factor. *(*Jemec 2003, Slade *et al* 2003)

Hormonal factors

Premenstrual flare-ups, female preponderance, frequent occurrence after menarche, improvement during pregnancy drew the attention toward hormonal factors and hypothesized hyperandrogenic syndromes. The usual absence of clinical signs of virilism, the normality of circulating androgens (Barth *et al* 1996, Lumnis *et al* 1995), the absence of hyperseborrhea (Jemec *et al*, 1997[b]), and the limited effect of anti androgen treatments, rule out a key role of hyper androgenism. (Jemec 2003).

Immunological and other host factors

No hard data on such factors are available but the association with Crohn's disease may open a track to be followed.

Epidemiology

Prevalence

Important discrepancies between studies make difficult to have a clear idea of the prevalence. Figure of 1/3000 has been proposed without specify neither the time frame nor diagnostic criteria (Fitzsimmons *et al* 1984). A systematic examination of patients in a dermatological department disclosed a rate of 1/1000 undiagnosed HS patients (Lookingbill 1988). A peak prevalence of 4% in a population of young adults in Denmark was recorded and would make HS one of the most frequent skin diseases (Jemec *et al* 1996[d]). These discrepancies are likely due to the fact that HS is most prevalent in young adults. A yearly prevalence of 1% in the general population based on subjects' recollection evidences also the high prevalence of HS. (Jemec *et al* 1996[d]). If such figures are exact the discordance with the apparent rarity in clinical experience could be explained by the prevalence of mild forms, the weariness of patients discouraged by the results of treatments and by the poor knowledge of HS in the medical community, which is revealed by the diagnostic lateness (frequently several years).

The sex ratio are variously estimated: women are three times more frequently affected, in genito-femoral areas while there is a clear predominance of men in the peri-anal region ; both sexes are equally affected in the axillary regions (Jemec *et al* 1996[a] , 1996[b])

Risk factors

Obesity is not associated with HS. However, when it is present, it may aggravate HS through mechanical irritation, occlusion and maceration. Tight clothing may also contribute to discomfort (Jemec *et al* 1996[c]). Cosmetics, shaving, depilation, use of talc have been suspected but they have been ruled out (Jemec *et al* 1988, Morgan *et al* 1982). Smoking is significantly more common in HS patients than in controls (König *et al*, 1999). Until now, no specific mechanism can explain this association. Whether it is a triggering factor or a consequence of the disease burden is still unknown.

Treatment

Severity grading

The classical 3 clinical stages as defined by Hurley (Hurley 1989) are:

- Stage 1: Single or multiple abscesses formation, without sinus tracts and cicatrisation.
- Stage 2: Recurrent abscesses, with tract formation and cicatrisation. There may be single or multiple widely separated lesions.
- Stage 3: Diffuse or near diffuse involvement or multiple interconnected tracts and abscesses are observed across the entire area.

This classification is useful at least as a guide to choose between medical or limited surgical treatment (stage1) and large excisional surgery (stage3). A new scoring system has recently been proposed which may be useful as an outcome index (Sartorius *et al* 2003). Pain scale and/or a quality of life scale may also be useful especially for clinical trials.

Therapeutic strategy: medico-surgical management

Treatment depends on the stage, evolvement of the disease and on the goal of the patient. A permanent cure can only be obtained by wide surgical excision but such a procedure is to be considered only in case of advanced disease *i.e.* stage III or severe stage II. Alternatively early disease may benefit of milder medical and/or surgical approaches.

Medical and surgical treatments are not mutually exclusive. On the contrary combination, simultaneously or successively, is often necessary.

Acute stage treatment options

Some patients suffer from recurrent painful nodules with no spontaneous tendency to open but also experience periods of remission. They may benefit from the following options:

- Topical treatments including antiseptics and antibiotics are not helpful due to the depth of the lesions although topical clindamycin has been claimed to be effective in a clinical trial against tetracycline. (Jemec *et al* 1998).
- A short course of antibiotic may be tried to shorten the pain duration and to avoid evolution of the lesion toward an abscess. Various antibiotics have been used for that purpose: amoxicilline, cephalosporine, clindamycine, rifampicin, M type penicillin. Their usefulness in that indication is questionable. The duration of an episode does not seem to be shortened (Von der Werth *et al.*, 2000[a]).
- Intralesional steroids (*e.g.* triamcinolone (5-10 mg) has been advocated. Rapid involution (12-24 hours) of early lesions has been claimed.

- High doses of systemic steroids may be used to reduce inflammation and pain. They have to be tapered rapidly.
- Incision and drainage with or without subsequent antibiotics is often necessary. It alleviates pain immediately and allows the evacuation of pus. Depending of the localization general anesthesia can often be avoided.

Chronic relapsing stage

Drug therapy
Various drugs have been used on a long-term, the goal is to stop the evolution, reduce the relapse rate and avoid pain and chronic suppuration. Most of them are disappointing when all the patients are considered. However, due to a probable heterogeneity of the disease, one particular patient may benefit from a drug, which is useless in most of the others. So it's worth to try each drug during several months.
- Antibiotics: Long term administration of tetracycline –alike what is done in acne- gives noticeable results. Clindamycin, rifampicin, the association of both, metronidazole particularly in case of bad odor, may be helpful. Each antibiotic can be used for 3-6 months but should be replaced regularly by another one. When surgery is indicated for stage III or severe stage II disease, a one-month course of antibiotics prior to surgery is useful to prevent infectious complications.
- Antiandrogens: Cyproterone acetate, associated with estrogens is useful only at very high doses *i.e*. 100mg/day. A relapse is observed at 50-mg (Mortimer *et al* 1986). It is not always well tolerated. At lower dosage, 2 mg associated with 30 µg ethynil estradiol in a contraception pill it is usually useless. Finasteride has been used in two patients (Farrell *et al* 1999)
- Rétinoïdes: Isotrétinoïne is usually very poorly effective (Boer *et al* 1999) in contrast to what is observed in acne. The absence of hyperseborrhea in HS may explain the difference (Jemec *et al* 1997). Cases in which HS is associated with nodular acne may be more responsive (Harms 1983). Some reports of successful treatment with etretinate or acitretin have been published (Hogan *et al* 1988, Chow *et al* 1922). All retinoids are highly teratogenic and the treatment may be difficult to manage in a female population of childbearing age.
- Dapsone has been used in 5 patients with good results after a short course of 2-4 weeks. Such a drug should be used with caution owing to its very serious side effects. (Hofer *et al* 2001)
- Anti TNF drugs: Several case reports and short series (Sullivan *et al* 2003) have claimed a dramatic efficacy of Infliximab which was first used in a patient having both HS and Crohn disease. A systematic study is worth to be done.

Radiotherapy
Several series of patients have been treated with radiotherapy. Doses up to 8 gray have been delivered with a 175 kV. In a recent series, complete relief of symptoms was obtained in 38% of patients and an improvement in 40% with no side effect on short term. (Frohlich *et al* 2000) The spontaneous high risk of cancer, especially skin cancers in perineal and buttocks of HS patients has been reported. So this potentially carcinogenic treatment should be considered with caution.

Surgical treatment (Slade et al 2003, Jemec 2003)
It has to be performed by an experimented surgeon, aware of the difficulties and failures occurring quite enough in HS.

Minor procedure
- Local excisions and primary closure: When the extent of skin involvement is limited, especially in case of relapsing abscess and suppuration of the same nodule, a local excision can be done. the morbidity is then lower but recurrence in the vicinity are frequent. The risk of insufficient excision with postoperative suppuration is to be taken into account.
- Exteriorization and laying *open* of tracts may be an alternative therapy; recurrence may occur.

Radical excision and healing with secondary intention or graft
It is the best option in stage III. The extent of excision must be enough wide and deep to remove all suppurative lesions and tracts, and also if possible all apocrine glands to avoid recurrence. Using starch/iodine/oxytocin may help to delineate the limits. (Parks *et al* 1997) Mapping of sinus tract with methyl violet intra operatively is useful. Primary closure is possible in the axilla but may lead to limited mobility of arms. Secondary closure is mandatory in genital and perianal locations. It may be done by graft or flaps. Transitional colic derivation may be necessary to allow healing in peri-anal location. Recurrences may occur either because of insufficiently wide excision or because of the presence of apocrine glands in aberrant location. The recurrence rate after wide excision is less than 30%.

Lasers
CO_2 laser excision is used in mild to moderate disease with secondary healing. Superiority in comparison with a classic surgery is a matter of debate. (Lapins *et al* 2002). Laser depilation to

prevent new lesions is an investigative procedure in early mild HS.

Unresolved questions

They are numerous:
- The pathophysiological nature of the disease.
- The usefulness of Infliximab and its role in the therapeutic strategy
- The relationship with Crohn' disease.
- The definition of therapeutic strategies adapted to the severity, the extent, the course, the location needs a medicosurgical approach by an expert team enable to take into account the progress in the management.

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