Hidradenitis Suppurativa: Clinical Studies Focusing on Evaluation

Karin Sartorius
Department of Dermatology, Södersjukhuset, Stockholm and Section of Dermatology, Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden. E-mail: karin.sartorius@sodersjukhuset.se

Karin Sartorius defended her PhD thesis on April 23, 2010, at Karolinska Institutet, Södersjuhuset, Stockholm. The examiners were Mats Berg, Uppsala University, Klas Nordlind, Karolinska Institutet, and Per-Erik Engström, Karolinska Institutet. The supervisors were Lennart Emtestam, Karolinska Institutet, Jan Lapins, Karolinska Institutet, and Gregor Jemec, University of Copenhagen.

Hidradenitis suppurativa (HS) is a chronic inflammatory disease of mainly unknown aetiology, which in most cases involves the axillae or groin and which can last for decades (6). This thesis studied different clinical aspects of HS: a modified clinical scoring system for evaluation of disease severity and treatment methods; disease severity in relation to smoking and obesity; outcome of carbon dioxide laser surgery; bacteraemia in patients with HS; and distribution of the neuroendocrine marker protein gene product (PGP) 9.5 in HS skin biopsies. The general aim of the research was to develop an objective scoring system for HS, but also to study some aspects of potentially pathogenic events in HS.

Karin Sartorius when defending her thesis at Karolinska Institutet. *Left to right:* Mats Berg, Jan Lapins, Karin Sartorius, Lennart Emtestam, Klas Nordlind and Per-Erik Engström.

Smoking and obesity are frequent among patients with HS and are considered plausible risk factors. A strong association between prevalence of HS and current smoking, as well as with high body mass index (BMI), has been found. In addition, correlation between increased BMI and severity of HS has been described. In recent years more attention has been paid to HS and new therapies are being discussed, which requires tools to measure disease activity and treatment outcome. Traditionally, the Hurley clinical grading system, with three stages, ranging from localized inflammation to fulminant disease, has been used to grade HS. Hurley stage I consists of one or more abscesses with no sinus tract or cicatrisation, and stage II consists of one or more widely separated recurrent abscesses with a tract and scarring. The most severe cases (stage III) are described as having multiple interconnected tracts and abscesses throughout the entire affected area. Hurley clinical grading is well suited for classification or staging, and may serve as basis for choice of treatment. However, for clinical trials it is important to have a more dynamic and detailed scoring system that is able to reflect disease activity and treatment effect in a local region, even if another region has developed in a different way. A further important aspect is that the majority of patients with HS seeking help from dermatologists are cases graded as Hurley stage II, and within this group there is a wide variation of clinical findings and symptoms, from milder cases with comparatively minor problems to the more severe cases that may have debilitating symptoms. This led to the development that started a few years ago, of a proposed scoring system (5). This system has been upgraded continuously since then.

The objective of the first study was to evaluate the modified Hidradenitis Suppurativa Score (HSS) and to study the impact of BMI and smoking habits on disease severity (1). Points were given for regions, types of lesion (nodules, fistulas), total area involved, and whether lesions were separated by normal skin. A positive correlation of fair degree between HSS and Dermatology Life Quality Index (DLQI) was found, as well as significant higher median scores in more advanced HS, in smokers compared with non-smokers, and in obese women compared with those of normal weight, respectively. The group of non-smoking patients in this study had significantly lower median HSS compared with the smokers, and with the group who had stopped smoking in between. The DLQI, in that respect, not did discriminate between the three groups. Overweight is another proposed risk factor. In this material, BMI was positively, but weakly, correlated with HSS, and when

divided into BMI classes the obese group had higher median score values compared with the overweight patients, who in turn had higher medians compared with the normal weight patients. This was a trend for the material as a whole, as well as for the women, but not was true for the men, perhaps because of the relatively small number of males included. As for smoking, the DLQI did not reveal any significant differences between the three weight groups, which suggests that a new scoring system is needed for such purposes. The main findings of this study were that HSS was positively correlated with Hurley stage, with smoking and obesity, and fairly well correlated with DLQI (1). The results indicate that the HSS reflects disease severity and draws out relevant information from HS patient material. Another important issue is the reliability of the tool, which can be investigated by measuring the interobserver variability when scoring the same set of patients. This has recently been performed in 23 patients with HS, by four observers, and showed a high factor of concordance and low interobserver variability (7). The HSS is designed primarily for clinicians who are particularly interested in HS. HSS may be suitable as a scoring method in clinical trials, since it correlates with existing scores and potential risk factors. There are some limitations in the use of HSS. Firstly, we have noticed that, for the most severe cases, with widespread disease that affects large skin areas, the difficulty in determining HSS increases, since it is hard to define single lesions if they are coalescing. Secondly, the degree of inflammation of individual lesions, or regions, is not included in the score, which would be valuable in particular for descriptive studies or studies of non-surgical therapy. Over time, in the same patient, the grade of inflammation can vary a lot, from silent periods with relatively dry sinus openings and non-inflamed nodules, to flare-up periods with pronounced erythema, oedema, suppuration and painful inflamed nodules. Work is in progress among a European network of dermatologists with special interest and expertise in HS to further improve the assessment of HS severity.

A number of treatments exist, based on whether HS is regarded as an infection, a type of acne, or a separate inflammatory disease (6). Treatments with immunosuppressive agents, anti-inflammatory drugs, antibiotics and oestrogens are of value in some patients. Currently, curative treatment consists mainly of surgery, but adjuvant medical treatment is often needed, and is, in many cases, appropriate as single therapy. The selection of treatment modality depends on several factors, including HS stage, anatomical location, frequency of exacerbation and the patient's condition and preference. The use of carbon dioxide laser treatment followed by secondary intention healing in HS was first described in 1987. The carbon dioxide laser emits a beam at a wavelength of 10,600 nm, which is absorbed by biological tissues. It can be used with a small-diameter spot size to cut, or a broad-diameter spot to vaporize, tissue. In HS cases the aim is to achieve complete radical ablation of diseased tissue, combined with preservation of healthy tissue. The procedure is facilitated and made safer by the microprocessor-controlled flash scanner that ablates the tissue in an even and controlled manner. In addition, thermal diffusion can be reduced if the laser energy is delivered to the tissue for less than the thermal relaxation time, by scanning the laser beam rapidly over the tissue area in a spiral-type pattern that maintains laser exposure of any spot to less than a millisecond, thereby reducing the risk of necrosis or thermal injury of adjacent tissue. Healing time by secondary intention after carbon dioxide laser of HS has been reported to be 3–8 weeks, although some cases of delayed healing may occur.

In the second study, scanner-assisted carbon dioxide laser treatment with subsequent healing by secondary intention was evaluated in 34 patients with HS, with in total 67 operating sites (2). Patients were interviewed by telephone about recurrences and end results, after a mean follow-up time of 34.5 (range 7–87) months. Four patients had had recurrences in one of the treated areas. In 12 cases, lesions had developed separated from the initial surgical site by >5 cm. Twenty-five patients had flare-ups of HS lesions in another anatomical region. Eight had no symptoms of HS during the follow-up period. Mean healing time was 4 (range 3–5) weeks. The conclusion was that, in chronic HS of Hurley grade II, scanner-assisted carbon dioxide laser treatment is an efficient treatment, which is well accepted by patients (2).

The clinical relevance of bacterial findings in HS is controversial (6). The bacteria are sometimes considered contaminants from the normal skin flora or as secondary infection in a previously sterile process. Interpretation of the results of bacteriological examinations from the surface of HS lesions is obscured by the possible contamination of resident skin bacteria. Bacterial cultures from HS lesions are often polymicrobial and have a predominance of anaerobic bacteria.

The objective of this study was to determine the number and type of bacteria circulating in the bloodstream in patients with HS undergoing carbon dioxide laser surgery (3). Blood samples were taken before, during and after surgery in 21 patients with HS Hurley stage II, and from five healthy controls. Bacterial growth in the first blood sample was found in nine patients, from the second in ten and from the third in six. In one patient, bacteria were detected in all the three samples. The dominating bacteria were Coagulase-negative staphylococci, of which most were subtyped as *S. warneri*. In six patients all samples were negative. We concluded that the carbon dioxide laser vaporization treatment of HS did not seem to cause any additional spread of bacteria into the bloodstream (3). The evaluation of cultures containing microorganisms from nor-

mal skin flora is always difficult. Since the bacteria detected in this study accord with those obtained previously in cultures from deeper parts of HS lesions, they seem to be relevant. The results should be interpreted with caution; however, growth of bacteria in the first blood sample taken before surgery could indicate that some of these patients have bacteria continuously circulating in the blood (3). Therefore more and larger studies should be carried out in patients with HS.

Knowledge is sparse regarding involvement of the neuroendocrine system in HS, but in light of the knowledge that certain neuropeptides play an important role in the pathogenesis of inflammatory skin diseases, it could be assumed that they are also engaged in HS. There are several markers for the neuroendocrine system. One is the general neuronal marker protein gene product (PGP) 9.5, which is found in neurons and nerve fibres of central and peripheral nervous system, many neuroendocrine cells, renal tubules, spermatogonia, Leydig cells of the testis and ova. The presence and distribution of PGP 9.5 has been studied previously in various dermatoses, but not in HS.

In the last paper of this thesis, the presence and distribution of the nerve fibre-marker PGP 9.5 was investigated using immunohistochemistry (4). Biopsies were taken from the groin or axilla of 16 patients with HS and 12 healthy controls. The median number of PGP 9.5-positive profiles was decreased in lesional epidermis, yet was statistically significant only in the groin. A similar difference was found in lesional dermis of the axilla, whereas in the lesional upper dermis of the groin the median number of profiles was increased. Cells with strong PGP 9.5 immunofluorescence were few or absent in epidermis, but significantly increased in lesional dermal skin of the groin. Thus, an imbalance of the PGP 9.5 immunoreactive nerve fibre profiles and PGP 9.5-positive cells by immunohistochemical staining, compared with controls, was demonstrated in this study. In conclusion, despite several study limitations, the findings indicate that PGP 9.5 positive nerve fibres could be involved in the pathogenesis of HS (4). The functions of the nerve fibres and the PGP 9.5-positive cells are not known. Both regarding the profiles and the cells, further efforts must be made to show whether these differences are primary events, or secondary to, for example, chronic inflammation, which is considered a major issue in HS. In addition, the origin of the cells needs to be investigated further.

In summary, patients with HS have a high degree of morbidity as measured by the DLQI. To evaluate this in an objective manner, in addition to the established Hurley staging system, a new clinical score has been proposed and is shown to correlate both with other scores and with risk factors for HS. Treatment with carbon dioxide laser seems to give satisfactory results and is not shown to spread bacteria during treatment sessions. Involvement of bacteria in HS is disputed, and knowledge about this is limited. This is also true for other pathogenic mechanisms. The presence and role of neuroendocrine-immune system elements, such as nerve fibre profiles and cells, in HS remain to be further mapped and investigated. Future studies of the aetiological mechanisms may provide new targeted opportunities to amend the therapeutic arsenal available to deal with HS. Early treatment might then further improve the quality of life, and ultimately the disease outcome, for patients with HS.

List of original publications

1. Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol 2009; 161: 831–839.
2. Lapins J, Sartorius K, Emtestam L. Scanner-assisted carbon dioxide laser surgery: a retrospective follow-up study of patients with hidradenitis suppurativa. J Am Acad Dermatol 2002; 47: 280–285.
3. Sartorius K, Lapins J, Jalal S, Emtestam L, Hedberg M. Bacteraemia in patients with hidradenitis suppurativa undergoing carbon dioxide laser surgery: detection and quantification of bacteria by lysis-filtration. Dermatology 2006; 213: 305–312.
4. Sartorius K, Emtestam L, Lapins J, Johansson O. Cutaneous PGP 9.5 distribution patterns in hidradenitis suppurativa. Arch Dermatol Res 2010; 302: 461–468.

Related publications

5. Sartorius K, Lapins J, Emtestam L, Jemec GBE. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol 2003; 149: 211–213.
6. Kurzen H, Kurokawa I, Jemec GB, Emtestam L, Sellheyer K, Giamarellos-Bourboulis EJ, et al. What causes hidradenitis suppurativa? Exp Dermatol 2008; 17: 455–472.
7. Sartorius K, Killasli H, Heilborn J, Jemec GBE, Lapins J, Emtestam L. Interobserver variability of clinical scores in hidradenitis suppurativa is low. Br J Dermatol 2010; 162: 1261–1268.