MEDICAL PRACTICE

Clinical Topics

Mediation of hidradenitis suppurativa by androgens

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Abstract

Forty two women with hidradenitis suppurativa were assessed clinically and biochemically for evidence of androgen excess. Thirteen had irregular menses; 22 of 36 experienced exacerbation of hidradenitis suppurativa premenstrually; 19 had or had had acne vulgaris; and seven were hirsute. Comedones (blackheads) were found in apocrine sites in 37, but also in retroauricular sites in 18 and were considered to be an important physical sign for early diagnosis. Eight had evidence of pilonidal (postanal) sinus. The patients had a higher concentration of total testosterone ($p<0.01$) and free androgen index (testosterone to sex hormone binding globulin concentrations) ($p<0.01$) than normal controls.

Patients with hidradenitis suppurativa appear to have endocrine abnormalities sufficient to suggest an androgenic basis for the disease.

Introduction

Hidradenitis suppurativa is a chronic cicatrising suppurative disorder of the regions bearing apocrine glands. Experimental reproduction of the disease by Shelley and Cahn showed that it is a poral occlusion disease with the added element of bacterial infection.[1] Although the sequence of pathological events is clear, the underlying causes are still not evident. Hurley stated, "an individual predisposition, perhaps hormonally induced, may be required. Certainly the frequent association with acne vulgaris, also a poral occlusion disease, suggests this."[2]

The association with acne vulgaris,[3-5] which is now established as a condition dependent on androgen,[6] and the failure of hidradenitis suppurativa to develop before puberty,[7] the general decline in disease activity seen at the climacteric, and the improvement seen during pregnancy,[8] all suggest a condition dependent on hormones. It is surprising, therefore, that there has been no systematic investigation of endocrine state in hidradenitis suppurativa. Chalmers *et al*, in a report describing hidradenitis suppurativa and acne vulgaris as presenting features of acromegaly, commented that endocrine factors in hidradenitis suppurativa had received scant study.[9]

We undertook to study the hormonal, and in particular androgenic, influences in hidradenitis suppurativa. From a series of 42 women we documented clinical data and examined hormonal biochemistry in an attempt to evaluate the endocrine basis of this disease.

Patients and methods

Forty two women with recurrent "blind boils" in skin bearing apocrine glands were assessed for signs of androgen excess. Patients (aged 15-59, mean 32·0 years) gave a history of disease activity ranging from a minimum of six months to 27 years (mean 8·5 years). Age at onset ranged from 11 to 43 years (mean 23·3 years; median 19 years): 25 had been aged 11-20; six 21-30; seven 31-40; and three 41-50. Axillary disease occurred in nine patients, genitocrural sites were affected in 15, and both axillary and genitocrural sites were affected in 18. Other sites affected included the submammary region (three cases), perineum and buttocks (one), labia (one), and ear lobes (one). Particular attention was paid to any history of irregular menses, infertility, cyclical flare of the disease with menses, and effect of pregnancy and treatment with oral contraceptives. All sites bearing apocrine glands were examined for evidence of disease. In addition, signs of virilisation, past or present acne vulgaris, hirsutes, and pilonidal sinus were sought.

Biochemical analysis—Forty one blood samples were analysed for concentrations of total testosterone, sex hormone binding globulin (performed

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using the Farmos sex hormone binding globulin immunoradiometric assay test kit), dehydroepiandrosterone sulphate, prolactin, gonadotrophins (follicle stimulating hormone and luteinising hormone), and 17-β oestradiol. Blood samples from 25 normal controls and 37 patients with idiopathic hirsutism, all matched for age, were obtained for comparison. In addition, haemoglobin concentration, white cell count, and blood glucose and immunoglobulin concentrations were estimated in the patients with hidradenitis suppurativa.

Statistical analysis was with the Wilcoxon rank sum test.

Results

CLINICAL DATA

Endocrine factors—Thirteen patients noted irregular menses as defined by missed periods or the start of menses consistently being more than five days adrift from the expected date. This figure is high but probably within the limits of normal prevalence.[10] Twenty two of 36 patients (the remaining six patients had had hysterectomies but not oophorectomies) noted exacerbation, enlargement, and increased tenderness of abscesses with or without increased purulent discharge immediately before the start of menses. The flare invariably occurred during the week before menses and usually two to three days before. Five patients (11%) had been investigated for infertility compared with a prevalence of true biological infertility in the general population of 3%.[11] Of the six patients who had had hidradenitis suppurativa during childbearing, five had noticed improvement during pregnancy and five had noted exacerbation, sometimes severe, after delivery. There appeared to be no definite relation of hidradenitis suppurativa to treatment with oral contraceptives. No patients showed evidence of systemic virilisation. Nineteen (45%) patients had or had had acne vulgaris compared with under 10% in a control population,[12] and seven (16%) were hirsute—that is, scored >10 in the Ferriman and Gallwey grading system—compared with under 2% in a control population.[13]

Comedones—Open comedones (blackheads) were found in 37 patients, usually in diseased areas but also in distant sites bearing apocrine glands that were unaffected by hidradenitis suppurativa. Comedones were often single or few in number and not necessarily overlying or close by the site of recurrent abscesses. Of interest was the relatively high prevalence of ear lobe (retroauricular) comedones and cysts. Our attention was drawn to this site, which is not considered to be an apocrine area, only when one patient complained of recurrent suppuration from her ear lobes, paralleling activity of her hidradenitis suppurativa elsewhere. Of 31 patients examined for evidence of retroauricular comedones, 18 possessed them. In a control group of 50 normal women matched for age only two had comedones in either apocrine or retroauricular sites.

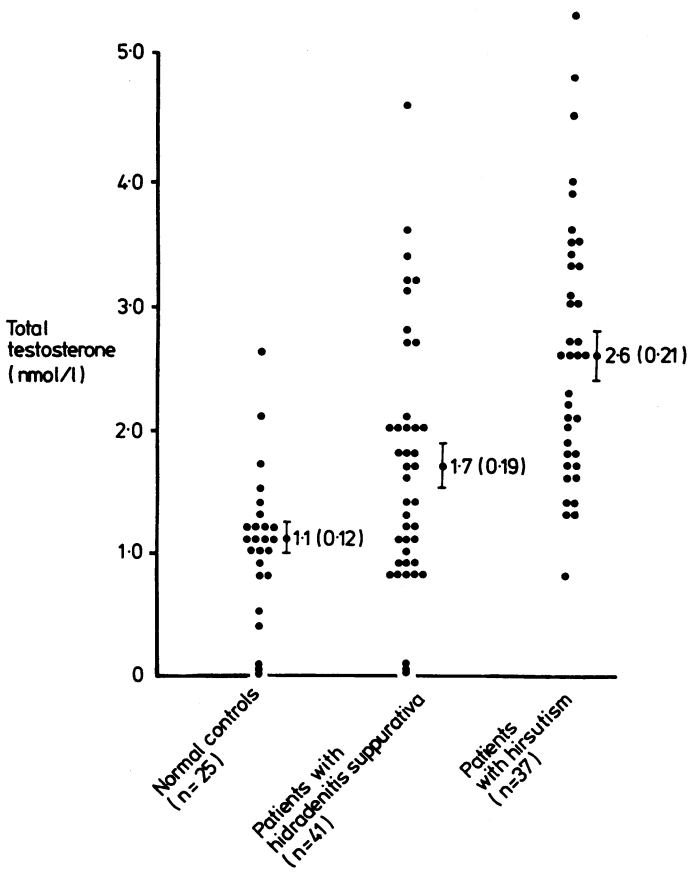

FIG 1—Distribution of total testosterone concentrations, with medians (and SE of medians).

Conversion: SI to traditional units—Testosterone: 1 nmol/l≈0·29 ng/ml.

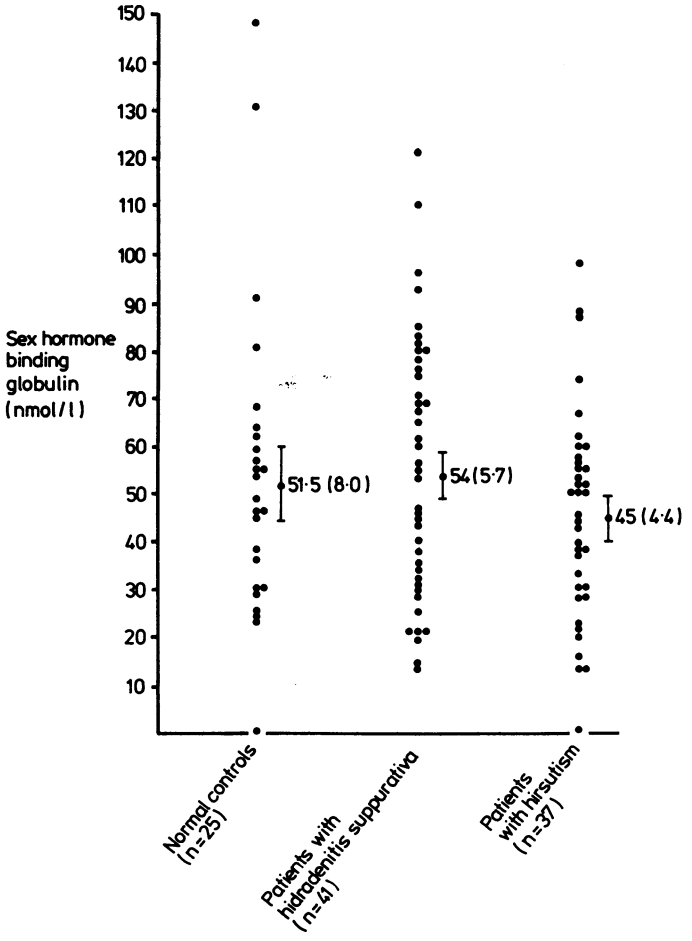

FIG 2—Distribution of sex hormone binding globulin concentrations, with medians (and SE of medians).

Pilonidal sinus—Eight patients had evidence of pilonidal sinus. All had received surgical treatment, and only two had suffered recurrence. In all cases the pilonidal sinus had not been considered to be related to hidradenitis suppurativa and had been managed independently. This compares with an incidence of one pilonidal sinus in every 3700 patients referred to the Mayo Clinic.[14]

BIOCHEMICAL FINDINGS

The distributions and ranges of concentrations of testosterone and sex hormone binding globulin in the patients with hidradenitis suppurativa and patients with hirsutism were different from those in normal controls (figs 1-3). Plasma testosterone concentration was significantly higher in the patients with hidradenitis suppurativa ($p<0·01$) and hirsutism ($p<0·001$) than normal controls (table). Dehydroepiandrosterone sulphate concentrations were not significantly different in the patients with hidradenitis suppurativa from those in the controls but were significantly higher in patients with hirsutism ($p<0·001$). Concentrations of sex hormone binding globulin were not significantly different between the three groups. The free androgen index (the ratio of testosterone to sex hormone binding globulin concentrations) was significantly higher in the patients with hidradenitis suppurativa ($p<0·01$) and hirsutism ($p<0·001$) than the normal controls. No significant differences in prolactin, thyroxine, follicle stimulating hormone, luteinising hormone, and 17-β oestradiol concentrations were found between the three groups. Haemoglobin, glucose, and immunoglobulin concentrations and white cell count were all within the normal range in the patients with hidradenitis suppurativa.

Discussion

Hidradenitis suppurativa presents to general and plastic surgeons, gynaecologists, and dermatologists. On occasions physicians are consulted when an underlying systemic disease is considered or an explanation for apparent recurrent infection is sought. The disease is often at an advanced stage before it is diagnosed, by which time undermining abscesses and sinus tracts have become established. The magnitude of the social, economic, and medical problems confronting patients is not generally recognised.[15] Medical treatment is disappointing, and radical surgery is the only chance of ensuring an immediate cure. Without surgery the natural progress of the disease is for it to grumble on with recurrent episodes of apocrine "boils" and chronically discharging sinuses. Although the disease can become spontaneously quiescent at an early stage, it more commonly continues relentlessly for years until the climacteric. Rarely does it progress beyond this period, and there are no reports of cases developing after the climacteric.

Apocrine glands are under hormonal control.[16] Secretion of sweat begins at puberty, the eventual peak of activity being reached during adult sexual life. After the climacteric secretory function wanes with diminution in the amount of apocrine sweat and size of glands. This hidradenitis suppurativa parallels the activity of the apocrine glands in not developing before puberty and declining after the menopause. Apocrine glands have cystic activity that is greatest during the premenstrual phase and lowest in the midmenstrium, although some authors refute this.[16] Nevertheless, this would help explain the premenstrual flare of hidradenitis suppurativa and tends to incriminate high progesterone concentrations with their potential androgenic effect, although other important metabolic changes occur during this time. Pregnancy produces relief for most patients with hidradenitis suppurativa and often dramatic improvement in Fox-Fordyce disease,[8] a response that strongly suggests decreased apocrine secretory activity during this period, presumably as a result of high oestrogen concentrations. Conversely, delivery often results in exacerbation. Eunuchs and eunuchoids do not develop hidradenitis suppurativa or acne. Of interest is a case reported in which a flare of axillary hidradenitis suppurativa occurred with each androgen treatment in a eunuchoid.[7] None of our patients had evidence of systemic virilisation, and the fact that five of our 42 patients had primary infertility is of doubtful importance. Although one third of the patients had clearly irregular menstrual cycles, suggesting hormonal imbalance, control data on the prevalence of irregular menses show wide normal variation depending on age, making conclusions difficult to draw.[10]

We found comedones in apocrine sites to be common in hidradenitis suppurativa, occuring in 90% of our patients. In acne vulgaris comedones are considered to be the hallmark of the disease, yet they are by no means always present.[17] Androgens are considered to be instrumental in the development of comedones, but the exact mechanism remains unclear. The existence of plugged follicles in hidradenitis suppurativa has been accepted histologically since Shelley and Cahn's original work on the pathogenesis of the condition,[1] yet nobody has commented on their importance as a physical sign. Highet *et al* mentioned that "the frequent presence of comedones in affected areas suggests an underlying structural abnormality of the pilosebaceous unit."[18] Comedones can arise in damaged skin—for example, extensive solar elastosis—and can be seen in scarred areas, but they can also be found at an early stage of the disease in affected and unaffected sites, including distant skin bearing apocrine glands. An interesting finding in our series was the high prevalence of comedones on the ear lobe, which is not considered to be an apocrine site; this is further evidence of a generalised tendency for apopilosebaceous plugging.

Frequent but anecdotal mention has been made of the association of pilonidal sinus with hidradenitis suppurativa. Jackman and McQuarrie commented that hidradenitis suppurativa is not uncommonly confused with pilonidal sinus and proposed that recurrent pilonidal sinus was probably an example of hidradenitis suppurativa.[19] The fairly strong association in our patients suggests that pilonidal sinus and hidradenitis suppurativa are related diseases, sharing the same basic pathogenesis—that is, apopilosebaceous blockage.

Many cases of the chronic debilitating form are the result of failure to diagnose and treat early disease. Awareness of its existence and, more importantly, recognition of initial clinical features are the

Median (SE of median) concentrations of plasma testosterone, sex hormone binding globulin, and dehydroepiandrosterone sulphate and free androgen index (ratio of testosterone to sex hormone binding globulin concentrations) in patients with hidradenitis suppurativa and normal controls and patients with hirsutes matched for age

	No in group	Testosterone (nmol/l)	Sex hormone binding globulin (nmol/l)	Free androgen index	Dehydroepiandrosterone sulphate (μmol/l)
Normal controls	25	1·1 (0·12)	51·1 (8·0)	0·019 (0·003)	5·1 (0·55)
Patients with hidradenitis suppurativa	41	1·7 (0·19)*	54 (5·7)	0·029 (0·022)*	5·5 (0·53)
Patients with hirsutism	37	2·6 (0·21)**	45 (4·4)	0·06 (0·008)**	7·1 (0·62)**

Significance compared with normal controls: *p<0·01, **p<0·001.
Conversion: SI to traditional units—Testosterone: 1 nmol/l≈0·29 ng/ml. Dehydroepiandrosterone sulphate: 1 μmol/l≈0·04 mg/100 ml.

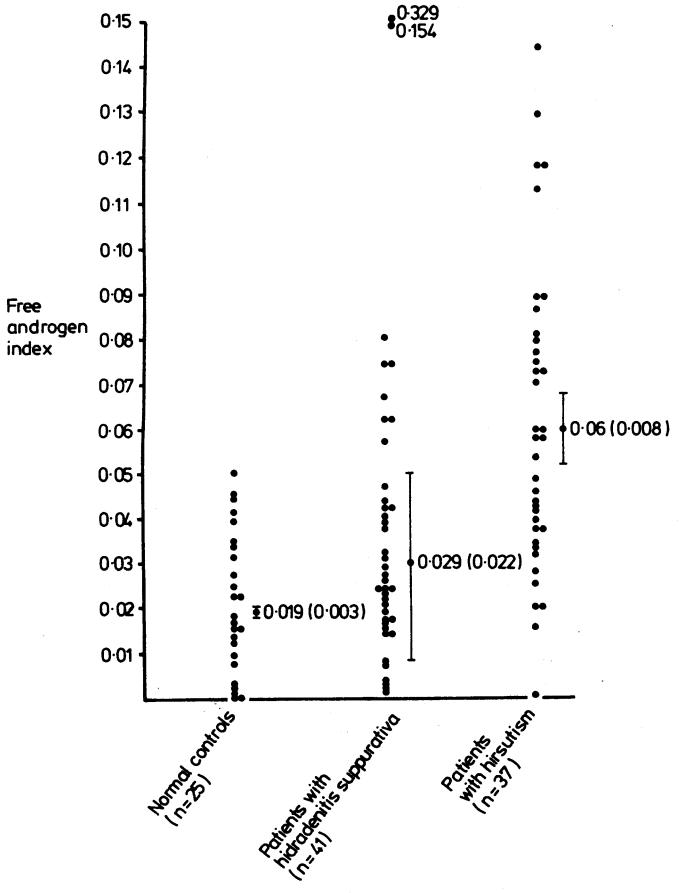

FIG 3—Distribution of free androgen index (ratio of total testosterone to sex hormone binding globulin concentrations), with medians (and SE of medians).

main reasons for this error. We suggest the following clinical criteria for diagnosis. Major criteria are (1) recurrent deep seated inflammatory nodules in skin bearing apocrine glands persisting for a minimum period of three months, not always discharging or fluctuating, and with a tendency for cord like coalescence; and (2) comedones in skin bearing apocrine glands and the ear lobes. Minor criteria include an association with acne vulgaris and, in women, exacerbation with menses.

Clinical data supporting the concept of an endocrine basis for hidradenitis suppurativa seem substantial. The possibility that the underlying defect might be due to an abnormality in available plasma androgens, as would appear to be the case in acne vulgaris[6] and idiopathic hirsutism,[20] prompted an endocrine screen in our patients. They had a higher concentration of total testosterone ($p<0{\cdot}01$) and free androgen index ($p<0{\cdot}01$) than a group of normal controls without cutaneous signs of androgen excess matched for age. Several patients with hidradenitis suppurativa had coexistent hirsutism or acne, but after correction for this by exclusion of these patients the total testosterone concentration and free androgen index were still significantly higher than those in the controls. Total testosterone concentrations and free androgen index were not as high as those in a group with hirsutism. Of interest was the fact that concentrations of sex hormone binding globulin were similar in all three groups, although they were lower in the group with hirsutism and approaching significance. Estimation of total testosterone concentrations has not been considered sensitive enough to detect the more subtle changes in biological activity that occur in conditions of benign androgen excess.[20-22] This is because even small increases in testosterone can reduce sex hormone binding globulin, thereby causing a relatively large increase in biologically active free steroid. This, however, has not been our experience, and our results may reflect differences in methodology—that is, our technique measured actual concentrations of sex hormone binding globulin whereas most previous studies have used assays measuring sex hormone binding globulin capacity.

Patients with hidradenitis suppurativa appear to have endocrine abnormalities sufficient to suggest an androgenic basis for this disease. Our results support the view that the basic defect might be an abnormality in available plasma androgens, but equally there may be an excessive rate of conversion of androgens within the gland to a more active androgen metabolite or an exaggerated response of the gland to a given hormonal stimulus. In this way hidradenitis suppurativa falls into the same category as acne vulgaris and idiopathic hirsutism as an example of primary cutaneous virilism[23] and therefore endocrinologically represents a heterogeneous group, with no single endocrinological abnormality determinable in every patient. Diagnosis, before undermining sinus tracts and burrowing abscesses have developed, is crucial for satisfactory control of the disease. Identification of comedones in affected and non-affected apocrine sites, as well as retroauricular areas, is important for early recognition. Past or present acne vulgaris and pilonidal sinus may be helpful pointers towards a diagnosis of hidradenitis suppurativa. Medical treatment including antiandrogen treatment should be beneficial providing it is given at an early stage in the disease before deep seated infection has become established.

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CLINICAL CURIO

Accurate recall of the date of injury in medicolegal cases

Studies of patients after injury suggest that a claim for compensation may be associated with a delay in the expected rate of recovery.[1-3] Patients may complain of continuing disability and be unresponsive to the various treatments offered, and thus it is important for the doctor to know whether a claim is pending.

One hundred patients aged 16-60 were studied to examine the hypothesis that those who can spontaneously quote the date of their injury are almost invariably seeking compensation.[4] All were attending hospital with persistent musculoskeletal symptoms after an injury sustained three months to three years previously. All were asked to recall the exact date of injury and, later in the consultation, to state whether they had made a claim for compensation.

Forty six patients remembered the date of their injury; 39 of these patients had been injured in non-sports accidents and 28 of these (72%) had a claim pending. Only three of 28 patients (11%) who could not remember the date of their injury and had had comparable accidents were seeking compensation. Twenty eight (90%) of the 31 patients with a claim pending remembered the date of their injury compared with only 18 (26%) of the 69 without such a claim. None of the 33 patients with a sports injury claimed compensation, though seven (22%) could remember the date of their injury.

Accurate recall of the date of injury is thus a helpful, though not infallible, pointer to a claim for compensation having been made after non-sports accidents. In such cases the date acquires special importance as patients need to quote it to solicitors and others dealing with the claim. Direct questioning about compensation at too early a stage in the consultation may be resented; asking the exact date of injury is a little known but useful alternative.—P E L EVANS, Guy's Hospital, London SE1.

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