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Does psychiatric illness affect the recurrence rate of genital herpes?

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SUMMARY The progress of 58 patients with first attacks of genital herpes was monitored for up to 30 weeks. The effect of sex (gender), age, social class, and non-psychotic psychiatric illness (as measured by the "general health questionnaire," GHQ) on the recurrence rate of herpes was studied. The recurrence rates, measured by the actuarial percentage recurrence-free curves, showed that the 29 patients with GHQ scores above 11 had a significantly higher recurrence rate than those who scored less than 11 ($P = 0 \cdot 002$). There were no important differences between recurrence rates according to sex, age, or social class.

These findings suggest that non-psychotic states, such as anxiety or obsessionality resulting in GHQ scores above 12, may possibly cause an excess production of adrenergic substances which encourages reactivation of latent genital herpes. Thus, to lessen the recurrence rate in such patients, a psychological or chemical approach to treatment could be used to modify the autonomic sympathetic response.

Introduction

Recurrences of genital herpes are painful and worrying and may be precipitated by various factors, including sexual intercourse, menstruation, and the emotional state of the patient.[1] Clinical episodes of recurrent herpes seem to be more common in male than in female patients,[2] and a recurrence is more likely if the primary attack was due to type 2 rather than type 1 virus.[3] Our experience suggests that patients who experience minor depression, anxiety states, feelings of inadequacy, and hypochondriasis have a first recurrence sooner than euthymic patients.

The "general health questionnaire" (GHQ)[4] measures non-psychotic psychiatric illness over the few weeks before interview, a high score indicating a high possibility of such illness. The GHQ is not a personality test; it has been validated both in general practice[5] and in the medical outpatient department of a general hospital.[4] GHQ scores have been shown to correlate well (+ 0·8) with psychiatrists' independent assessments and correctly identify 95% of patients thought to be psychiatrically ill at interview. The questionnaire is self-administered and consists of 60 questions about feelings and behaviour. The patient scores one for each symptom experienced "over the past four weeks," so that the total score may range from 0 to 60. The questionnaire takes approximately 15 minutes to complete. Patients with scores in excess of 11 are defined as "potential psychiatric cases" (although they may have overt illness). Using the GHQ as a quantitative assessment of the mental state of the patient, we tested the hypothesis that the rate of recurrence of genital herpes after the primary attack was higher in patients with pre-existing psychiatric illness than in those without.

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Patients and methods

STUDY POPULATION

One hundred and thirty male and female patients seen at the department of genitourinary medicine, University College Hospital, London, between June 1979 and June 1980 who had their first clinical attack of genital herpes confirmed by culture were considered for entry into the study. They were excluded if any of the following criteria were satisfied: they could not reattend or keep in touch by post (four patients); they had a past history of genital herpes (eight patients); they spoke insufficient English to answer a questionnaire (two patients);

they were married (in a small-pilot survey married patients were unwilling to have postal inquiries sent to them) (10 patients); they had painless genital ulcerations (one patient with early syphilis); they were homosexual men with painful anorectal ulceration (12 patients); they had ulceration and had returned from Africa or the Far East in the preceding three months (two patients); or they had concomitant genital disease, for example gonorrhoea, chlamydial infection, trichomoniasis, candidosis, or warts (30 patients). Three patients refused to take part in the study.

The nature of the study was explained to the potential participants and their informed consent obtained to complete the GHQ and for follow-up inquiry by letter. Age, occupation, and sex of the 58 patients who were eligible to take part in the study were recorded. Those who agreed to take part were told to bathe the lesions frequently with saline. No antiviral agents were used.

INITIAL EXAMINATION

Serum from the genital ulcers was transferred on alginate swabs (Medical Wire and Equipment Co Ltd, ref: MW-104) into virus transport medium,[6] refrigerated at 4°C for not more than four hours, and transferred on to a cell culture system[7] to isolate herpes simplex virus. The isolates were not typed. Serum from the ulcers was also examined by dark-field microscopy for *Treponema pallidum*. Serological tests (rapid plasma reagin and *T pallidum* haemagglutination assay[8]) were routinely performed to exclude syphilis.

The 60-item GHQ[4] was explained to the patients, who were asked to complete it alone in a side-room. Patients were told that if they failed to reattend for follow up, their progress would be monitored by a postal questionnaire.

FOLLOW-UP INVESTIGATIONS

Dark-field microscopy was repeated twice in the following seven days and again at two and four weeks after the initial examination if the ulcers had not healed. Serological tests were repeated at four weeks and again at three months after the initial visit for patients who reattended. Patients who returned to the clinic because of painful genital ulceration had further cultures performed for herpes simplex virus, repeat dark-ground microscopy to exclude *Treponema pallidum,* and repeat serology for syphilis.

Postal inquiries were sent out at 14 and 28 weeks after the inital visit to patients who had not reattended. These asked about recurrence (including date) of genital sores during the period from the first visit. Reminder letters were sent out at 16 and 30 weeks to the patients who did not respond to the postal inquiries. Personal letters were sent to the 13 patients who still failed to reply.

STATISTICAL ANALYSIS

For each patient the period from the first clinic visit to either recurrence or the date last known to be recurrence-free was calculated to the nearest week. The date of recurrence was defined as the date of virologically confirmed recurrence in those patients who reattended the clinic and the date of first appearance of symptoms of recurrence (as recorded by the patient on the postal questionnaire) in those patients who did not reattend the clinic.

The actuarial percentages recurrence-free[9] at weekly intervals after the initial clinic visit were calculated for various subdivisions of the sample. The resulting percentage recurrence-free curves were compared using the logrank test.[9] The distributions of GHQ scores in the subgroups of patients with recurrence confirmed by culture, recurrence not confirmed by culture, and no recurrence at 28 weeks were compared using the Kruskal-Wallis[10] one-way analysis of variance by ranks. Comparisons of these distributions in any two subgroups were made using the Mann-Whitney U statistic.[10]

Results

Thirty-seven women and 21 men with primary genital herpes took part in the study and 29 (50%) reported a recurrence within 28 weeks of attendance. Seven of these 29 (24%) patients returned to the clinic during the 28 weeks because they had painful genital ulceration; all were culture-positive. Recurrence was not confirmed by culture in the remaining 22 patients who did not reattend the clinic.

Of the 29 patients who did not report recurrence of genital herpes, 16 (55%) stated in response to a postal questionnaire that they were recurrence-free 28 weeks after the initial visit, five (17%) were recurrence-free at 14 weeks but did not respond to the questionnaire at 28 weeks, and the remaining eight (28%) patients were lost to follow-up after their initial attendance for the primary attack. These eight patients all attended for at least the first week after the initial visit but did not reply to the postal inquiries at 14, 16, 28, and 30 weeks or to a personal letter.

For the total of 58 patients there were no important differences between the actuarial percentage recurrence-free curves for the two sexes (logrank test $\chi_1^2 = 0{\cdot}39$, $P = 0{\cdot}53$), for the three age groups (<24, 25-34, 35 years, and over) ($\chi_2^2 = 2{\cdot}1$, $P = 0{\cdot}34$), or the five social classes ($\chi_4^2 = 1{\cdot}1$, $P = 0{\cdot}89$). The 29 patients with a GHQ score above 11 had a significantly higher recurrence rate than the

29 patients with a GHQ of 11 or less (logrank test $\chi_1^2 = 9 \cdot 9$, $P = 0 \cdot 002$). The actuarial percentage recurrence-free curves for these two groups are shown in the figure.

The characteristics of three subgroups of patients (recurrence confirmed by culture, recurrence unconfirmed by culture, and recurrence-free at 28 weeks from entry) are summarised in the table. The distributions of GHQ scores in these three groups were significantly different (Kruskal-Wallis test $\chi_2^2 = 10 \cdot 8$, $P = < 0 \cdot 01$). Subsequent analysis by the Mann-Whitney test indicated that the group without recurrence at 28 weeks had lower GHQ scores than the other groups ($P < 0 \cdot 01$ in both comparisons); there was no important difference between the distributions of GHQ scores in the two recurrence groups ($U = 76 \cdot 5$, $P = 0 \cdot 98$).

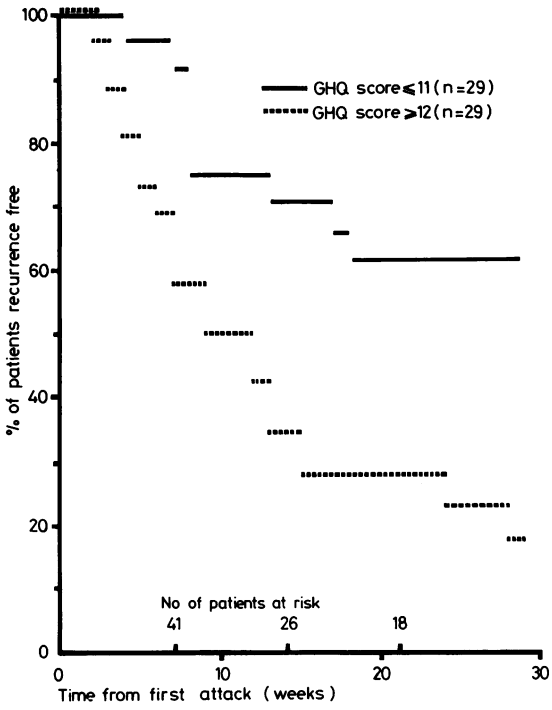

FIGURE *Actuarial percentage recurrence-free curves.*

Discussion

Although the isolates were not typed it seems from the present study there is no association between age, sex, social class, and time to recurrence of genital herpes. The recurrence rate in potential psychiatric cases (those scoring 12 or over on the GHQ), however, was significantly greater than the 'normals' (11 or less). Similarly, the GHQ scores of patients with recurrences were significantly greater than those who felt they did not have a recurrence during the 28 weeks of the study.

Because the GHQ is a measure of hypochondriasis as well as depression and anxiety, it may be argued that the group with recurrence unconfirmed by culture would be likely to feel they had a recurrence when in fact they did not. There was no important difference, however, between the distribution of the GHQ scores in the subgroups with recurrence confirmed by culture and recurrence unconfirmed by culture. We consider this, together with the identical subjective feeling of disease relapse, to be evidence in favour of these two groups being similar psychologically and in terms of mode of clinical

TABLE *Summary of characteristics of patients with recurrence of genital herpes and patients with no recurrence at 28 weeks from entry to study*

	Recurrence		
	Confirmed by culture	*Not confirmed by culture*	*No recurrence at 28 weeks**
No of patients	7	22	16
Sex			
Male	3	7	7
Female	4	15	9
Social class			
I	1	5	3
II	2	9	4
III	2	6	7
IV	2	1	1
V		1	1
Age (years)			
Range	21-38	18-38	19-41
Median	23	24·5	23
GHQ score			
Range	7-50	0-46	0-26
Median	18	22·5	5

*The 5 patients with no recurrence by 14 weeks and the 8 lost to follow-up are excluded from this table.

recurrence. Thus, most of the patients with recurrence unconfirmed by culture would have been culture-positive if they had revisited the clinic at the time of apparent recurrence.

The results of this study suggest that ongoing potential non-psychotic psychiatric illness contributes towards reactivation of latent genital herpes. This of course assumes that the GHQ score in any one patient remains essentially static up to the time of recurrence. Juel-Jenson[11] has stated that 'emotional upset' may be a factor causing reactivation of latent infection 'possibly due to release of adrenaline.' Recurrences of herpes simplex encephalitis and keratitis are known to be precipitated in rabbits by the administration of parenteral adrenaline.[12 13] In many of the states, such as anxiety or obsessionality, which result in a patient having a GHQ score over 12, an excess production of adrenergic substances may possibly encourage clinical relapse of genital herpes. Modification of autonomic sympathetic response, whether by psychological or chemical means, may thus lessen the recurrence rate in patients who experience recurrences of genital herpes and who have minor non-psychotic mental disability.

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References

1. Hutfield DC. Genital herpes. *Br J Vener Dis* 1968;**44**:241-50.
2. Corey L. Clinical epidemiology and clinical course of genital herpes simplex virus infection. In: *Non-gonococcal Urethritis and other Sexually Transmitted Diseases of Public Health Importance.* Report of WHO Scientific Group, WHO Technical Report Series No 6600. Geneva: WHO, 1981:21-30.
3. Corey L, Stamm W, Reeves WC. Controlled trial of BCG vaccination for the prevention of recurrent genital herpes. *Antimicrobial Agents and Chemotherapy, 1976.* Bethesda, Maryland: American Society for Microbiology, 1979.
4. Goldberg DP. *The Detection of Psychiatric Illness by Questionnaire.* Oxford: Oxford University Press, 1972.
5. Goldberg DP, Blackwell B. Psychiatric illness in a suburban general practice. A detailed study using a new method of case identification. *Br Med J* 1970;**2**:439-43
6. Stokes EJ, Ridgway GL. In: *Clinical Bacteriology,* 5th ed. London: Arnold, 1980; 365.
7. Herrman EC, jun. Experiences in laboratory diagnosis of herpes simplex, varicella zoster and vaccinia virus infections in routine medical practice. *Mayo Clin Proc* 1967;**42**:744-53.
8. Stokes EJ, Ridgway GL. In: *Clinical Bacteriology.* 5th ed. London: Arnold, 1980; 274-83.
9. Peto R, Pike MC, Armitage P, *et al.* Design and analysis of randomised clinical trials requiring prolonged observation of each patient. II Analysis and examples. *Br J Cancer* 1977;**35**:1-39.
10. Siegal S. *Non-parametric Statistics for the Behaviour Sciences.* New York: McGraw-Hill, 1956.
11. Juel-Jenson BE. A new look at infectious diseases. Herpes simplex and zoster. *Br Med J* 1973;i:406-10.
12. Tokumaru T, Scott TFM. The herpes virus group; herpes virus hominis, herpes virus simiae, and herpes virus suis. In: Lennette EH, Schmidt NJ, eds. *Diagnostic Procedures for Viral and Rickettsial Diseases.* 3rd ed. New York: American Public Health Association Inc, 1964; 381-433.
13. Laibson PR, Kibrick S. Reactivation of herpetic keratitis by epinephrine in rabbits. *Arch Ophthalmol* 1966;**75**:254-60.