HERPES SIMPLEX VIRUS TYPE-2 IN CARCINOMA CERVIX: A CONTROLLED SEROLOGICAL STUDY

by

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Sero-epidemiological and cytological studies have indicated that infection with herpes simplex virus type-2 possibly has an important role in carcinoma cervix (Naib *et al* 1973; Josey *et al* 1976; Rawls *et al* 1970; Nahmias *et al* 1970 and Belsey and Adler, 1978). Cytological studies in patients with carcinoma cervix have revealed a high rate of changes compatible with herpes simplex virus infection (Kotcher *et al* 1962). Viral nucleic acids (Frankel *et al* 1972) and virus related antigens (Aurelian, 1973) have been detected in the cervical tumour cells. Christian *et al* (1975) were able to isolate herpes simplex virus from the malignant lesion. However, in general, virus induced tumours do not readily yield the virus due to the tendency of the virus to remain in an accult form (Josey, 1976).

Realising the present uncertainty regarding the aetiology of carcinoma cervix, particularly its relationship with infection with herpes simplex virus type-2 and the paucity of Indian studies on the problem, it was thought worthwhile to undertake the present study with the aim to investigate the relationship between herpes simplex virus type-2 infection and cervical cancer.

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Material and Methods

Hundred patients with cervical lesions were randomly selected from among those attending the O.P.D. and/or admitted to the wards of Queen Mary's Hospital, K.G's. Medical College, Lucknow. Of these, 36 proved to be having various stages of carcinoma cervix, the remaining 64 being labelled as having chronic cervicitis with or without erosion. Seventy cases without evidence of any cervical disease served as controls. Serological examinations for herpes simplex virus type-2 were carried out in all the three groups of the cases in different dilutions—ranging from 1/4 to 1/64, by complement fixation test in microtitre system (Lennette and Schmidt, 1964).

Observations

As can be seen from Table I, there was a marked difference between the cancer group on one hand and the cervicitis and control groups on the other. The test was negative (titres upto $\frac{1}{4}$) in only 2 (22.2%) cases of cancer compared to nearly 57%

TABLE I

Antibody Titres for Herpes Simplex Virus type-2

Group	Complement fixation test titres									
	Upto 1/4 (—ve)		1/8 (+ve)		1/16		1/32		1/64	
	No.	%	No.	%	No.	%	No.	%	No.	%
Carcinoma cervix (36)	8	22.2	13	36.1	11	30.6	3	8.3	1	2.8
Chronic cervicitis (64)	37	57.8	19	29.7	8	12.5	—	—	—	—
Controls (70)	40	57.2	24	34.3	5	7.1	1	1.4	—	—

of the cases in the other two groups. Furthermore, the titre was much higher in cases of carcinoma. Age had no effect, the titre being almost same below and beyond 40 years of age.

The antibody titre had a definite relation with socio-economic class (Table II). It was more frequently positive and in higher titres in the lower class in all the three groups of patients. The test was positive in all the cases having more than one sexual partner and in more than 1/16 or more dilutions in all the 4 prostitutes. However, domicile and religion had no effect.

Discussion

There was a marked difference between the cancer cases and those with non-malignant crvical conditions. The test was negative (titres upto ¼) in only 8 (22.2%) of the cases of carcinoma compared to nearly 60% of the patients in the other two groups. Moreover, the titre was much higher in cases of carcinoma. The test was more frequently positive and in higher dilutions in patients of lower socio-economic class and in patients with more than one sexual partner. All the prostitutes had 1/16 or more titre.

Case controlled studies have demonstrated significantly more neutralising antibodies to herpes simplex virus type-2 in patients with cervical cancer than in controls (Nahmias *et al* 1974; Adams *et al* 1974; Josey *et al* 1976 and Lahiri *et al* 1978). There can be three explanations for this difference between the occurrence of antibodies in patients of cancer and in controls (Mumford *et al* 1978). Firstly, the herpes virus may be a secondary invader in already formed cancer. Secondly, the factors of sexual activity associated with carcinoma cervix might also place a person at high risk for contracting a venereal infection. It may be that the real carcinogen is related to sexual promiscuity which predisposes an individual to the carcinoma. Thirdly, the virus may act as carcinogen or a co-carcinogen.

Reasonably sufficient data are there to refute the first two possibilities. It has been seen that women develop herpes infection at an earlier age than cancer cervix. The mean ages, for dysplasia, carcinoma in situ and invasive carcinoma are 25, 31 and 48 years respectively, while the mean age for herpes infection is 20 years (Naib *et al* 1969). Nahmias *et al* (1970) followed up 870 women with herpes genitalis and 562 controls for one to six years. He found that carcinoma occurred eight times more commonly in

TABLE II

Socio-economic Classwise Results of Complement Fixation Test for Herpes Simplex Virus type-2

Group	Upper class			Middle class			Lower class			Total
	Total	Positive	%	Total	Positive	%	Total	Positive	%	
Carcinoma cervix	4	1	25.0	11	7	63.6	21	20	95.2	36
Chronic cervicitis	8	1	12.5	35	12	34.7	21	14	66.6	64
Controls	7	2	28.5	40	10	25.0	23	18	78.3	70

women with herpes infection than in controls. In addition, Catalano and Johnson (1971) demonstrated antibodies to herpes simplex virus type-2 in 35.7% of the women who went on to develop carcinoma in situ 1-8 years later and in only 7% of those who did not. These studies indicated that infection with the virus preceded the malignant changes in the cervix rather than following them. Similarly, the second possibility, i.e., cancer cervix and herpes infection are co-variables of sexual promiscuity, can also be refuted. Adams *et al* (1974) found that non-promiscuous cancer patients too had a higher incidence of antibodies and in higher titres than did non-promiscuous controls.

However, not all the cases with carcinoma cervix demonstrated the presence of antibodies to the virus and not all patients with the antibodies develop carcinoma. Herpes simplex infection cannot, therefore, be the exclusive cause of the disease. Other factors, viz., poor hygiene, multiparity, early coitus and promiscuity must be taken into account when discussing the aetio-pathogenesis of the disease.

To conclude, the evidence that relates herpes simplex virus type-2 to cervical carcinoma is quite suggestive although it is not definite. As a consequence it is still important to consider the risk of cervical carcinoma developing in patients with herpes virus antibodies. It can be said that patients with virus antibodies are upto 10 times more likely to develop invasive carcinoma than those without them (Mumford *et al*, 1978).

Summary

With the aim to study the relationship between infection with herpes simplex virus type-2 and carcinoma cervix, 36 cases with various stages of the disease

were compared with 64 cases of chronic cervicitis with or without erosion and 70 controls with non-cervical conditions. All the cases were subjected to complement fixation test for herpes simplex virus type-2 antibodies. The test was positive in more than three-fourths of cases of carcinoma cervix compared to less than half of those in the other two groups. Moreover, the titres of the antibodies were higher in cases of carcinoma. The titres were very much higher in patients from lower socio-economic class, in all the three groups. All the patients with more than one sexual partner had antibodies and the titre was still higher in all the prostitutes.

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