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RESEARCH ARTICLE

SEROPREVALENCE OF HERPES SIMPLEX VIRUS-2 IgG ANTIBODY IN PATIENTS WITH CARCINOMA CERVIX

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ABSTRACT

Cervical cancer is one of the most common cancers among women worldwide. Clinical observations and epidemiological studies on genital cancer have revealed an association with sexual behaviour thus motivating research into sexually transmitted agents which may be responsible for neoplasia. Herpes simplex virus-2 (HSV-2) infects the genital mucosa and establishes a lifelong latent infection in sensory ganglia. The observation that cervical carcinoma behaves like a venereally transmitted disease with a relatively long latency period has led to the suspicion that herpes simplex virus-2 might be its causative agent. In the present study, sera from 80 histopathologically diagnosed cases of carcinoma cervix were examined for IgG antibody by herpes simplex virus Type 2 recombinant Gg2 (IgG-ELISA) kit, manufactured by Nova Tec Immunodiagnostica, Gmbh, Germany. Among the 80 carcinoma cervix cases, 20% (16/80) were seropositive for herpes simplex virus-2 IgG antibody. Analysis according to histologic types of growth showed that all the positive cases were squamous cell carcinoma of cervix. None of the other types had antibodies to HSV-2.Serologic screening will help in early detection of high risk cases and help in prevention of carcinoma cervix.

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INTRODUCTION

The persistent infection with a high risk HPV is recognized as the principal factor for malignant progression of cervical lesion. However in some women infected since several years, there are no complications while others develop cancer. This factor suggests that other factors play an important role in the transformation process (Dongang *et al*., 2011). Epidemiologically both cervical cancer and herpes virus type 2 infections involve women with similar sexual lifestyles – an observation which is compatible with an etiologic role of the virus in the formation of malignancy (Rawls *et al*., 1968). The Emory university group first postulated in 1964 an association between *Herpes simplex* virus infection and cervical neoplasia (Adelusi, 1984). Women who have human papilloma virus (HPV) infection of cervix have a greater risk of invasive cervical cancer if they also have genital herpes, according to a pooled analysis of case control studies (Smith *et al*., 2002). HSV-2 infection increase susceptibility to HPV causing alterations of epithelial cells, thus facilitating the entry of HPV virions (Dongang *et al*., 2011). The most likely sequence of events in the genesis of cervical cancer is that exposure to HSV-2 is followed by an infection involving the stem cells in the transition zone of cervix.

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The viral DNA in the cells in some way prevents them from undergoing normal differentiation, and as they proliferate they develop first into mildly dysplastic lesions. With the passage of time, less differentiation occurs, the dysplasia becomes more severe, and eventually carcinoma in-situ results. After a number of years, the proliferating carcinomatous cells eventually penetrate the basement membrane of the cervical epithelium, resulting in invasive cervical carcinoma (Thomas *et al*., 1984).

Clues pointing to Oncogenicity of HSV-2 (Aurelian, 1973)

1. HSV-2 is transmitted by sexual contact and cervical cancer essentially behaves as a venereal disease.
2. HSV-2 is a ubiquitous human pathogen and causes latent infection.
3. Mean age for infection with HSV-2 precedes by 6 years mean age for development of preinvasive cervical cancer.
4. Causes chromosome aberrations similar to those described in cervical cancer.
5. Antigen characteristic of tumours present in cells infected with herpes simplex virus
6. Prevalence of antibody to HSV-2 in cases of atypia, carcinoma in situ and invasive cancer.
7. Presence of DNA fragments of HSV-2 in an invasive cervical carcinoma.

Glycoprotein G of HSV-1 and HSV-2 is highly immunogenic and shows very little cross reaction (Taylor, 2006). Therefore the detection of Gg-2 antibodies is a reliable indicator of past or present HSV-2 infection (Reddy *et al*., 2005).

The study was conducted to find the seroprevalence of HSV-2 IgG antibody in patients with carcinoma cervix and to find the possible correlation of different histopathological types of cancer cervix with seroprevalence of IgG antibody.

MATERIALS AND METHODS

Study group

The present study was conducted in a tertiary care hospital in Assam during a period of one year from June 2011 to May 2012. Blood samples were collected from clinically diagnosed patients with carcinoma cervix attending Gauhati Medical College and Dr. B. Borooah Cancer Institute, Guwahati and presenting with symptoms like bleeding per vagina (post-menopausal, intermenstrual, post-coital),vaginal discharge, pain in the lower back, leaking of urine or faeces. Informed consent from the patient and permission from Institute Ethics Committee were obtained. Histopathological confirmation was obtained from Pathology Department.

Inclusion criteria

80 histopathologically confirmed cases of carcinoma cervix who did not receive any treatment for carcinoma cervix were included in the study. Among 80 carcinoma cervix cases, 74 were squamous cell carcinoma, 5 were adenocarcinoma and only 1 was small cell carcinoma.

Collection of blood sample

Under all aseptic care, about 5 ml of blood was collected in a sterile vial from the carcinoma cervix patients. The vial was left at room temperature and the blood was allowed to clot for separation of serum. The serum was then separated by centrifuging the blood in a centrifuge machine at 3000 rpm for 5 minutes.

The separated serum was then transferred to a sterile vial, labelled and stored at -20˚C till the assay was done (as per ELISA kit). All the sera were examined by HSV Type 2 recombinant Gg-2 (IgG ELISA) kit, manufactured by Nova Tec Immunodiagnostica Gmbh, Germany.

RESULTS

Herpes simplex virus type 2 IgG antibody was detected in 20% (16/ 80) patients with carcinoma cervix. All the 16 HSV-2 IgG antibody positive cases were squamous cell carcinoma of cervix.

Table 1. Seroprevalence of HSV-2 IgG antibody by ELISA among carcinoma cervix cases

Carcinoma cervix cases	Seropositive	Seronegative
80	16 (20%)	64(80%)

Table 2. Prevalence of HSV-2 IgG in different histopathological types of carcinoma cervix

HSV-2 IgG	Squamous cell carcinoma	Adenocarcinoma	Small cell carcinoma
Positive	16	0	0
Negative	58	5	1
Total	74	5	1

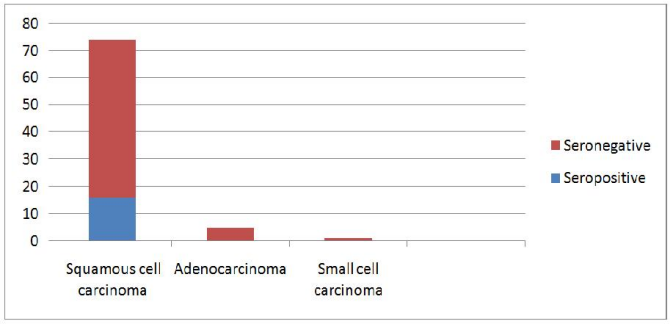

Figure 1. Prevalence of HSV-2 antibodies in different histopathological types of carcinoma cervix

Majority of the carcinoma cervix cases were aged between 41-50 years.Of the 16 HSV-2 IgG positive cases, 62.5%(10) had the history of giving 4-7 child births,75%(12) had sexual intercourse before 17 years of age, 56.25%(9) had multiple sexual partners and 68.75% (11) had no history of contraception.

Table 3. Risk factors associated with HSV-2 IgG positive carcinoma cervix cases

HSV-2 IgG +ve cancer cervix	Parity		Age at first sexual intercourse		Number of sexual partners		History of contraception	
16	≤3	5	≤17	12	1	7	Absent	11
	4-7	10						
			≥17	4	>1	9	Present	5
	≥8	1						

DISCUSSION

The association of cervical carcinoma with sexual activity has been known for over 150 years (Daraji *et al*., 2009). The search for the etiology of human tumours is complicated by the nature of the host. Evidence that virus could cause tumours in man has been entirely dependent on the knowledge accumulated from work with animal models (Aurelian, 1974). In the present study, 20% (16) of the carcinoma cervix cases tested positive for IgG antibodies by HSV-2 recombinant ELISA. This correlates well with the findings of the study carried out by Kjaer *et al*. (1993) and Ozaki *et al*. (1978) who reported a slightly higher prevalence of 26.6% and 28% respectively. A slightly lower prevalence of 17.1% and 8% were reported by Rawls *et al*. (1976) and Ibrahim *et al*. (2000) respectively by type specific ELISA. Analysis according to histopathological growth showed that all the 16 HSV-2 IgG antibody positive cases were squamous cell carcinoma of cervix. None of the other types (5 adenocarcinoma and 1 small cell carcinoma) had antibodies to HSV-2. Similar observations were made by Royston *et al*. (1970) and Adelusi *et al*. (1976) that genital

herpes was associated with squamous cell carcinoma of cervix. However, Seth *et al*. (1978) reported that HSV-2 infection did not vary according to histopathological types of carcinoma. Among the HSV-2 IgG antibody positive cases, 62.5% were women with higher parity, 75% had sexual intercourse at or before 17 years, 56.25% had multiple sexual partners and 68.75% did not use any contraceptive methods. Adam *et al*. (1972) also reported an increased occurrence of antibodies to herpes virus type 2 among women with the attributes of sexual and reproduction associated factors.

The demonstration of etiological role of herpes virus type 2 in cervical cancer would offer, through serologic monitoring, potentially effective methods of preventing the disease. Characterisation of women with high risk of cervical cancer by antibody tests would become feasible. The characterisation of high risk groups which could then be intensively followed with cervical cytology should lead to a substantial reduction in morbidity and mortality from cervical cancer beyond that presently realized.

Conclusion

A single infection of HSV-2 early in life may produce changes in cells of the cervical epithelium that could manifest after an appropriate latent period. Alternatively, the cancer could also develop in a stepwise fashion and reinfection or reactivation of the virus may be involved in the progression of the lesions. The demonstration of an etiologic role of HSV-2 would help in developing a vaccine to reduce the occurrence of the cancer. Results of the study also demonstrate the importance of HSV-2 serology in identifying the high risk individual. Therefore, serologic assay should be utilized in the mass screening of high risk population for the early detection and control of carcinoma cervix.

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