EXPRESSION OF HPV 16 AND 18 IN CERVICAL INTRAEPITHELIAL NEOPLASIA

Kodali Venkataramana[1], Prasad Usha[2]

[1]Assistant Professor, Department of Obstetrics and Gynaecology, Andhra Medical College, Visakhapatnam.
[2]Assistant Professor, Department of Obstetrics and Gynaecology, Andhra Medical College, Visakhapatnam.

ABSTRACT

BACKGROUND

Cervical cancer is by far the most common human papilloma virus related disease. Nearly, all cases of cervical cancer can be attributable to human papilloma virus infection. Infection with the human papilloma virus is the main risk factors for cervical intraepithelial neoplasia and cervical cancer especially the high-risk types.

The aim of the study is to study the prevalence of high-risk human papilloma virus 16 and 18 in various grades of cervical intraepithelial neoplasia.

MATERIALS AND METHODS

It is a prospective study for a period of two years. 50 cases of cervical intraepithelial neoplasia of various grades on histopathology were included in the study. Polymerase chain reaction DNA sequencing was done in all the cases. The patients were followed up for 1 year with Pap smears and results tabulated.

RESULTS

77.77% of cases were human papilloma virus 16 positive and 22.22% for human papilloma virus 18. High-risk human papilloma virus was positive in 66.66% of cases beyond 30 years of age. In cases with positive HPV 16 or 18, 62.5% of CIN 1 cases progressed to CIN 2 on follow up for one year,all the CIN2 cases progressed to CIN 3 and CIN 3 cases persisted in the same phase.

CONCLUSION

High-risk human papilloma virus testing beyond 30 years should be included in the screening test along with Pap smears.

KEYWORDS

Cervical Intraepithelial Neoplasia, Human Papilloma Virus 16, Human Papilloma Virus 18, Expression, Progression.

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BACKGROUND

Human Papillomavirus (HPV) is a DNA virus belonging to the Papillomaviridae family. There are more than a 100 types of HPV infecting humans. HPV may infect cutaneous or mucocutaneous tissue depending on its predilection.

Genital HPV infections are contracted through sexual intercourse, anal sex and other skin-to-skin contact in the genital region. Some HPV infections that result in oral or upper respiratory lesions are contracted through oral sex. The peak incidence of contracting HPV infection is shortly after becoming sexually active. Most of the times, the body's immune system is able to combat the infection. In some cases, infection persists and may cause warts and genital cancers. About a dozen, high-risk HPV types have been identified. Two of these, HPV types 16 and 18 are responsible for most HPV caused cancers.[1,2] Cancer cervix is mostly due to infection with high-risk HPV. Cervix cancer is the fourth leading cause of cancer-related death across the globe. In India, 1,22,844 women are diagnosed with cervical cancer and 67,477 die from the disease every year. According to the National Cancer Registry Program (NCRP), the most common sites of cancer among women are the breasts and the cervix. It usually takes 15 to 20 years before a precancerous lesion becomes invasive cancer, so effective cancer screening methods will be able to reduce cervical cancer-related deaths, especially in the developing countries.

Aim of the Study

To study the prevalence of high-risk human papilloma virus 16 and 18 in various grades of cervical intraepithelial neoplasia.

MATERIALS AND METHODS

It is a prospective study for a period of two years from June 2012 to June 2014. A total of 50 cases with diagnosis of various grades of dysplasia on biopsy were subjected to human papilloma virus DNA sequencing by polymerase chain reaction. The sequencing is done to detect high-risk human papilloma virus 16 and 18. Planned follow up was done every three months for a period of one year with Pap smears.

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Corresponding Author:
Dr. Prasad Usha,
Q No. 49-3-3, Lalithanagar,
Visakhapatnam-Pin 530016, Andhra Pradesh.
E-mail: ushaprasad411@gmail.com
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RESULTS

Total number of precancerous lesions studied was 50 cases. Cervical Intraepithelial Neoplasia (CIN) constituted 7.14% of cervical lesions. CIN 1 was 31 cases (62%), CIN 2 10 cases (20%) and CIN 3 9 cases (18%) (Table1). Eighty percent of cases presented with leucorrhoea, 14% were asymptomatic and 6% presented with postcoital bleeding (Table 2). 56% of cases had first sexual activity between 13 to 19 years of age in cases with cervical intraepithelial neoplasia (Table 3). 84% of cases with cervical intraepithelial neoplasia had microcytic hypochromic anaemia and grade of anaemia was more in CIN 3 lesions. Macrocytic anaemia was seen in 12% of cases (Table 4). Per speculum examination of cervix showed erosion in 60% of cases, hypertrophy in 36% of cases and normal in 4% of cases (Table 5).

Cervical intraepithelial lesions, 32% of cases occurred between 21-30 years of age, 34% in the age group 31-40 years, 20% in the age group 41-50 years, 10% between 51-60 years and 4% between 61-70 years. CIN 1 and 2 were more common between 21 to 40 years of age (Table 6). Out of 31 cases of CIN 1, 25.8% of cases showed presence of either HPV 16 or 18. Out of 10 cases of CIN 2, 50% of cases showed presence of either HPV 16 or 18. Out of 9 cases of CIN 3, 55.5% of cases showed presence of either HPV 16 or 18 (Table 7). 77.77% of cases were HPV 16 positive and 22.22% cases were positive for HPV 18. HPV 16 was more common in CIN 1 and HPV 18 in CIN 3. Combined expression was not seen in any of the cases (Table 8). High-risk HPV was positive in 66.66% of cases beyond 30 years of age and 33.33% positive in age below 30 years of age (Table 9).

During follow up for one year by Pap smear, 10 women discontinued and only 40 were available for Pap smear. The final outcome of CIN was classified as progression, persistence or regression. All CIN lesions with negative HPV 16 or 18 did not progress. In cases with HPV positivity for 16 or 18, 8 cases of CIN 1; 5 cases (62.5%) progressed to CIN 2 and all 5 cases of CIN 2 progressed to CIN 3 and CIN 3 cases persisted in the same phase.

Lesions	Number of Cases	Percentage
CIN 1	31	62%
CIN 2	10	20%
CIN 3	09	18%
Total	**50**	**100%**

Table 1. Distribution of Cervical Intraepithelial Lesions (n=50)

Clinical Presentation	Number of Cases	Percentage
Leucorrhoea	40	80%
Postcoital bleeding	03	6%
Asymptomatic	07	14%
Total	**50**	**100%**

Table 2. Clinical Presentation of Cervical Intraepithelial Lesions (n=50)

Age at First Sexual Activity	Number of Cases	Percentage
10-20 years	28	56%
20-30 years	12	24%
>30 years	10	20%
Total	**50**	**100%**

Table 3. Age at First Sexual Activity in Cases of CIN (n=50)

Anaemia	Number of Cases	Percentage
Microcytic hypochromic anaemia	42	84%
Macrocytic anaemia	06	12%
No anaemia	02	4%
Total	**50**	**100%**

Table 4. Anaemia in Cervical Intraepithelial Lesions (n=50)

Findings	Number of Cases	Percentage
Hypertrophy	18	36%
Erosion	30	60%
Normal	02	4%
Total	**50**	**100%**

Table 5. Per Speculum Findings in Cervical Intraepithelial Lesions (n=50)

Type of Lesion	21-30 Yrs.	31-40 Yrs.	41-50 Yrs.	51-60 Yrs.	61-70 Yrs.
CIN 1	11	10	8	4	1
CIN 2	4	5	1	1	1
CIN 3	1	2	1	-	-
Total	**16**	**17**	**10**	**5**	**2**

Table 6. Age Distribution of the CIN (n=50)

Lesions	Total Cases	HPV DNA Positive	HPV DNA Negative
CIN 1	31	08	23
CIN 2	10	05	05
CIN 3	09	05	04
Total	**50**	**18**	**32**

Table 7. HPV DNA Positivity in Various Grades of CIN (n=50)

Type of Lesion	Number of Lesions Positive for HPV DNA	HPV 16 Positive	HPV 18 Positive
CIN 1	08	07	01
CIN 2	05	04	01
CIN 3	05	03	02
Total	**18**	**14**	**04**

Table 8. Prevalence of HPV DNA (16, 18) in Various Grades of CIN (n=18)

CIN	HPV Positive	
	≤30 Years	**≥30 Years**
CIN 1	03	05
CIN 2	02	03
CIN 3	01	04
Total	**06**	**12**

Table 9. Prevalence of HPV in CIN Lesions with Respect to Age (n=18)

DISCUSSION

HPV infection of the cervix affects the developing immature metaplastic cells of the transformation zone. Cervical neoplasia develops by interaction of high-risk papillomavirus and immature metaplastic epithelium, once maturity occurs the risk of neoplasia decreases. Exposure to HPV is an extremely common in young sexually active women. Yet, despite frequent HPV exposure at that phase of life in which the cervical transformation zone is at its most vulnerable, established expressed disease is relatively uncommon. The progression rate from normal, but high-risk HPV-infected cervical epithelium to CIN 2 or 3 is higher. Despite this, most cervical abnormalities will not transform into invasive cancer, even if left untreated.

The long time lag between initial infection and eventual malignant conversion and spontaneous regression of many primary lesion suggests that the lesions can be detected at early stage. Potential cofactors like cigarette smoking, oral contraceptives, dietary deficiencies and chronic inflammation contribute to the acceleration of the neoplastic process. Although, most cervical cancers contain high-risk HPV types up to 15% of such cancers test negative for HPV raising the possibility that a few, usually more aggressive, cervical cancers may arise from a non-viral source.[3,4,5,6]

Carozzi FM et al[7] analysed- 144 CIN 2, 385 CIN 3. 6.9% of cases were HPV negative. The proportion of HPV 16/18 was 60.8%, 76.6% in CIN 2 and CIN 3, respectively (P trend = 0.004). Correnti M et al[8] analysed the cervical cancer burden in Venezuelan women and HPV types 16/18 was prevalent in 65% of cases with cervical intraepithelial neoplasia. Coutlee F et al[9] studied HPV status in Canadian women and HPV16 was the most common genotype in CIN. HPV18 was detected more frequently in adenocarcinoma than squamous cell carcinoma (P = 0.013). Sjoeborg KD et al[10] of Norway analysed 643 histologically confirmed cervical intraepithelial neoplasia grade 2 and CIN 3. Overall, HPV 16 or 18 were detected in 58.0% HPV16 was most common being detected in 51.2% of all cases. Jariene K et al[11] of all the women with cervical intraepithelial changes, 59% were positive for HR HPV and 62% were positive for HPV types 16, 18. PCR analysis of 47 cervical tissue specimens revealed HPV 16/18 infection in a total of 19 (40.4%) cases while 28 (59.6%) cases turned out to be HPV 16/18 negative. Among the high-risk HPV, 16/18 positive women, 4 out of 5 cases (80%; 4/5) were of 20-29 years, 7 out of 25 cases (28%; 7/25) were of 30-44 years and 8 out of 17 cases (47.06%; 8/17) were of ≥45 years of age. Individually, type 16 and type 18 were positive in 7 (14.9%) cases each and dual infection with type 16 and 18 were seen in 5 (10.6%) cases.[12]

In the present study, 77.77% of cervical intraepithelial lesions were HPV 16 positive and 22.22% cases were positive for HPV 18. HPV 16 was more common in CIN 1 and HPV 18 in CIN 3. Combined expression was not seen in any of the cases. High-risk HPV was positive in 66.66% of cases beyond 30 years of age and 33.33% positive in age below 30 years of age.

Maria Gabriela Loffredo D'Ottaviano et al-[13] CIN 2 regression rate was 49% (18/37), persistence as CIN 1 or CIN 2 was 22% (8/37) and progression to CIN 3 was 29% (11/37). Castle et al[14] found that the presence of HPV 16 was positively associated with CIN 3 and they reported that CIN 2 caused by HPV 16 maybe more likely to progress than CIN 2 caused by other high-risk HPV types.[15] Kjær et al[16] in a population study found that HPV 16 persistent infection was associated with high absolute risk for progression to high-grade cervical lesions. In the present study, all CIN lesions with negative HPV 16 or 18 did not progress. In cases with HPV positivity for 16 or 18, 62.5% of CIN 1 cases progressed to CIN 2 and all 5 cases of CIN 2 progressed to CIN 3 and CIN 3 cases persisted in the same phase.

CONCLUSION

In the present study, majority of cases with cervical intraepithelial neoplasia presented with white discharge and had first sexual activity between 13-19 years of age. Macrocytic anaemia was seen in 12% of cases. Cervical erosion was the common clinical presentation in the age group of 31-40 years. 77.77% of cases were HPV 16 positive and 22.22% for HPV 18. HPV 16 was more common in CIN 1 and HPV 18 in CIN 3. Combined expression was not seen in any of the cases. High-risk HPV was positive in 66.66% of cases beyond 30 years of age. All CIN lesions with negative HPV 16 or 18 did not progress. In cases with HPV positivity for 16 or 18, 62.5% CIN 1 progressed to CIN 2 and all cases of CIN 2 progressed to CIN 3 and CIN 3 cases persisted in the same phase. Hence, high-risk HPV testing should be included in the screening test along with Pap smears.

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