Review Article

Role of Human Papilloma Virus in Retinoblastoma- A Review

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ABSTRACT

Retinoblastoma (RB) is an intraocular tumor and the primary malignancy occurring in children. Untreated RB leads to the metastasis of central nervous system, optic nerve, bone marrow and lymphoid systems. The genetic etiology for RB formation is well established, but few studies have shown the strong association of infection or infectious agents and cancer formation. Especially the role of human papillomavirus (HPV) in tumorigenesis has been widely studied. This review emphasizes the role of HPV in RB formation; describes the mode of transmission of the virus to the embryo and lays out a platform to evaluate alternative strategies such as immunization of adolescents and screening of both the partners with suspected lesions to protect the child from RB tumor.

Keywords: HPV, Retinoblastoma, mode of transmission

Introduction:

Retinoblastoma (RB) is an intraocular tumor and the primary malignancy occurring in children. The incidence of the RB worldwide is 1 in 16,000 to 18,000 births.[1] Review of literature of RB cases in India shows that, 69% cases were unilateral and remaining were bilateral. The median age of the children suffering with RB was around 2.5 years with the male to female ratio of 1.6:1, showing male preponderance. A subset of 10 % of this intraocular tumor leads to the metastasis.[2]The clinical symptoms include leukocoria, strabismus, hypopyon, orbital cellulitis, hyphema, and exophthalmia.[2]

Untreated RB can lead to metastasis of the central nervous system, optic nerve, bone marrow and lymphoid systems. A study related to the cause of the specif c mortality in long time survivors of RB tumor was done which shows that in hereditary and nonhereditary retinoblastoma survivors, the relative rates of mortality following subsequent malignant neoplasm were higher in those who had undergone radiotherapy treatment.[3]

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Role of Genetic factors in Retinoblastoma

The genetic etiology for retinoblastoma formation is well established, involving the occurrence of the mutations in the RB1 gene.[4] Several studies related to the occurrence of the mutations in RB1 gene, leading to loss of its function and the development of the retinoblastoma tumor.5-9 A recent study revealed the correlation between parental intake of diet and development of retinoblastoma. This study has shown that father's intake of diary associated nutrients and use of calcium supplements associated with the decreased risk and intake of the copper, manganese, and vitamin E were associated with increased risk, while mother's use of multivitamins close to conception was associated with the decreased risk.[10]

Role of HPV virus in cancer genesis

There is a strong association of infection or infectious agents and cancer formation. Evan and Muller provided epidemiological guidelines to support the etiologic role of virus as a causative

agent of cancer. They hypothesized that geographic distribution of viral infection should coincide with particular cancer; detection of virus or viral markers should be high in tumor cases compared to normal subjects and antiviral treatment should reduce or decrease the tumor incidence. In addition to these other factors included were, virus should have an ability to transform cells in-vitro, viral genome should be demonstrated in the tumor tissue and last but not least, it should be able to induce tumor formation in experimental animals.[11] The oncogenic virus such as human papilloma virus (HPV) is known to induce cancer formation, through the interaction of genome of the host cells, alteration in cell cycle regulation, leading to the uncontrolled proliferation and carcinogenesis. HPV is an icosahedral DNA virus and it is very well established fact that it induces the formation of cervical cancer.[12] Studies also favored and supported the role of HPV in causation of head and neck squamous cell carcinoma[13], oral[14] and esophageal cancer.15 The HPV were classif ed as high risk HPV and low risk HPV, based upon the presence of early proteins E6 and E7 (Figure 1). These E6 and E7 interact and bind with the tumor suppressor genes like p53 and retinoblastoma pRb respectively, leading to their functional degradation and uncontrolled proliferation of cells leading to the carcinogenesis.[16]

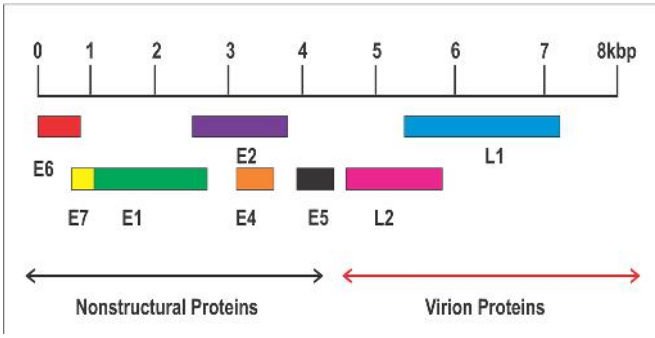

Fig. 1: Genome of Human Papillomavirus

HPV and retinoblastoma

There is a great deal of debate about the role of HPV in retinoblastoma formation. Literature studies supported as well as negated the etiology of HPV in the genesis of retinoblastoma tumor. There is a quite disparity in detection of HPV among different ethnical regions. The presence of the HPV in retinoblastoma tumor was demonstrated in 27.9% of cases in South American region.[17] Few Indian studies have shown the causal role of the HPV in retinoblastoma. A study conducted by Mohan et al[18] has demonstrated the presence of the HPV in fresh RB tumor samples by nested PCR using appropriate ocular controls and HPV positive controls and demonstrated HPV positivity in 47% of RB cases. Among them HPV16 was detected in 57% of tumors. Anand et al[19] has done a detailed study of detection of the HPV in prospective and retrospective cases and found HPV in 24% of RB cases of which 70% cases showed the presence of high risk HPV16, also this study for the f rst time detected presence of HPV 45,59,68 and 72. This study also showed that reduced expression of pRb, indirectly indicating the inactivation of pRb by the HPV E7 oncoprotein. Normally pRb inhibits the transcription of the cyclin-dependent kinase inhibitor gene $p16^{INK4a}$, but in this study they proved that the loss of expression of pRb leads to overexpression of $p16^{INK4a}$. Recently Naru[20] and coworkers have detected the presence of HPV16 in non-familial cases of retinoblastoma. Espinoza et al[21] has pointed out the presence of HPV6 and concluded that the presence of HPV acts as a cofactor in the progression of the RB through promoting nonrandom additional mutations.

Mode of transmission of human papillomavirus in RB might be

A low level of education, lack of barrier contraceptives increases the risk of the cervical HPV infection as well as birth of child with RB tumor. Bhuvaneshwari and coworkers[22] in their study showed that 3 RB samples harbored HPV16, HPV16 and 59, HPV16 and 73 correlated with the HPV16 in the respective mothers cervical brushing samples. This study clearly demonstrated the possible association of the HPV in RB formation as an alternative mechanism other than the mutations in RB1 gene. Similar study was done by Shetty et al[23] demonstrated the presence of high risk HPV virus in 69.7% of RB cases (n=76), and in 50% of the cases (n=10) had similar HPV status along with the corresponding maternal cervical cytology smear.

Orjuela et al[24] in RB tumor samples found increase presence of HPV 18 than HPV16 and this may be due to an increased oncogenic potential of HPV18 in retinal tissue. They also hypothesized that initial perinatal transmission of HPV was seen high in mothers infected with HPV18 compared to women infected with HPV16.

Another mechanism which might allow the HPV to the retinal cells is the presence of HPV in the paternal sperm cells. A study conducted by the Chan et al[25] demonstrated the presence of HPV sequences in the Percoll washed sperm cells. 64% of sperm specimens showed the presence of high risk HPV16 and 18 and suggested the possible role of sperm as a vector for HPV, similar results are echoed by the Lai et al[26] and they suggested that certain HPV genes are expressed actively in infected sperm cells and these virus infected sperm cells behave as vectors for transmission of HPV. Chan et al[27] demonstrated the transmission of the HPV DNA from the sperm cells to the uterus and embryo.

Several other studies from different parts of the world demonstrated the presence of HPV in retinoblastoma. Hector et al[28] demonstrated that not only high risk HPV are found in the RB cases, but also low risk HPV6 is found to be associated with the RB formation.

Contrary to the above results, several studies ruled out the role of HPV in the RB formation. A study conducted by Antoneli had demonstrated the prevalence of HPV DNA in RB cases was 4.6% and in normal control it was 9.1%, indicating low prevalence of HPV and they were unable to conclude the role of HPV in RB formation29 Howard and coworkers studied the role of DNA oncogenic viruses in the formation of RB but could not demonstrate the association.[30] A similar study was done by Gillison et al to correlate the role of DNA viruses including HPV, adenovirus and polyomavirus in the genesis of RB, but was not able f nd any pRb inactivating viruses in the RB tissue.[31] Ryoo et al from Korea screened for the presence of HPV16 in RB and found no causal relationship with retinoblastoma.[32]

Conclusion

Human Papillomavirus is termed as oncogenic virus and is one of the most commonly sexually transmitted infection. It has already proven its role in genesis of cervical tumor and other squamous cell carcinomas such a penile cancer. RB origin till now is known to be caused due to the mutations mainly in the RB1 gene. However recent studies have shown a profound relationship between the infectious agents and genesis of the cancer. Studies have shown the role as well negated the role of HPV in the genesis of the RB tumor formation. The presence or absence of HPV in RB mainly depends upon the epidemiology of HPV in that particular region, socio-economic conditions.

Future Perspectives

This review lays out a platform to evaluate alternative strategies to prevent retinoblastoma formation including the use FDA approved vaccines against HPV as studies have shown that RB tumor can be acquired from infected parents. We also propose that screening for HPV has to be done for both the partners who have suspicious lesions for the same to prevent the child from tumor formation. We emphasize that the role of HPV in the genesis of the retinoblastoma tumor has to be further investigated with appropriate control population.

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