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HUMAN PAPILLOMA VIRUS -6,16 IN THE PATHOGENESIS OF ORAL LICHEN PLANUS -A SYSTEMATIC REVIEW

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ABSTRACT **BACKGROUND;** Oral lichen planus (OLP) is a chronic inflammatory mucocutaneous disease . Human papilloma virus(HPV) -6,16 is seem to have significant relation with oral lichen planus.The Systematic review is to assess the presence of HPV-6,16 in the pathogenesis role of Oral lichen planus. Published literature on HPV-6,16 in Oral lichen planus from 1990–2016,were searched through PUBMED , MEDLINE and Google , performed.Articles were also selected by a hand search from the relevant journals .Finally ,a total of six relevant articles were reviewed. In our review , studies on HPV -16 in Oral lichen planus showed 17% positivity and studies on HPV -6 in Oral lichen planus showed 8% positivity . Results showed that HPV-6,16 do not have role in the pathogenesis of oral lichen planus. We can conclude from our review that Human papilloma virus - 6,16 cannot be detected in Oral lichen planus cases.

KEYWORDS

Assessment; Oral lichen planus ,Human papilloma virus -6,16, pathogenesis

ARTICLE HISTORY

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INTRODUCTION

Oral lichen planus(OLP) is common chronic inflammatory disease affecting 0.5 to 2.2 % of general population. Oral lichen planus commonly affects middle aged and has female predilection. The lesions appears as white plaque like striations,papular or erosive or atrophic or reticular.(1)

The etiology and pathogenesis of OLP are unknown though several molecular hypotheses have been presented. The etiology of OLP involves the degeneration of the epithelial basal cell layer, induced by cell-mediated immunologic reactions[2]

Histologically, oral lichen planus lesions shows hyperkeratosis, liquefaction of basal layer ,infiltration of lymphocytes in epithelium connective tissue interface. [3,4]. Unknown antigen may play a role for lymphocyte infiltration in this disease. It is also suggested that in OLP apoptosis is trigerred by autocytotoxic CD8+T cell[5] .Keratinocyte antigen expression might be altered by exogenous agents.In viral infections , virus acts as cytoplasmic antigen or induce the expression of host cell protiens,which causes altered host cell protein profile. The response of these specific CD8+T cells is similar to what occurs during a viral infection where a virus can act as a cytoplasmic antigen or induce the expression of host cell proteins, resulting in an altered host cell protein profile [6].

Human papilloma virus(HPV) are mostly associated with proliferative epithelial lesions due to their affinity towards squamous epithelial cells. HPV 16 and 18 by expression of E6 and E7 genes compromise physiological cell cycle control by binding of the related oncoproteins to the tumor suppressor gene products p53 and pRB [7,8].It is also found that HPV infection based on keratinization of tissue,that is keratinized tissue is more resistant to HPV infection[9].

Hence it has been suggested that Human papilloma virus(HPV) might play role in pathogenesis of Oral lichen planus[10]. HPV-16, HPV-18 and HPV-31, have an association with Oral lichen planus[11].
There fore this systematic review aimed to analyse Human papilloma virus (HPV)-6,16 in the pathogenesis of Oral lichen planus.

MATERIALS AND METHODS

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES:

The search strategy was in accordance with the Cochrane guidelines for systematic reviews .Articles relevant to the search strategy were identified from search data bases of PUBMED and MEDLINE till the year 2016.Due to limitation of number of articles on Human papilloma virus and Oral lichen planus ,no timeline was included for the search.The article search included only those from the English literature.An internet search was also done to obtain the relevant articles of our interest.The title of the articles and abstracts were reviewed.The full text of selected articles were retrieved and further analysed.

SEARCH METHODOLOGY:

The search methodology applied in PUBMED was using the following

keywords:
Search(((((((HPV6)OR Human papilloma virus 6))AND ((HPV 16) OR Human papilloma virus -16))) AND ((Pathogenesis)OR Pathological process))) AND ((((((((((((((((((((((((oral lichen planus) OR oral lichen ruber planus)) OR oral mucosal lichen planus)) OR oral autoimmune disease)) OR oral squamo papulous disorder)) OR oral papulosquamous disorder)) OR Oral mucocutaneous disease)) OR Oral inflammatory disease)) OR Oral potentially malignant lesion)) OR Oral precancerous lesion))OR Oral premalignant lesion)) OR Oral white lesion)) OR Oral potentially malignant condition)) OR Oral precancerous condition))OR Oral premalignant condition)

In addition ,an internet search was also done using the key words “Oral lichen planus” and “Human papilloma virus-6” and “ Human papilloma virus -16”

SELECTION OF STUDIES :

INCLUSION CRITERIA:

1.Original studies on Human papilloma virus-6,16 in Oral lichen Planus.
2.Ex vivo studies
3.Studies were the samples are obtained from the patients manifesting the disease in active state.
4.Studies done on tissue samples
5.Studies in English language were included

EXCLUSION CRITERIA:

1.Studies in animals models were excluded
2.Studies done with oral scrapings

DATA EXTRACTION AND OUTCOMES

Once the articles to be reviewed were finalized, data was extracted from each article, tabulated and was verified and interpreted (Fig-1) The outcomes assessed in this review examined and analysed the role of Human papilloma virus-6,16 in the pathogenesis of Oral lichen planus.

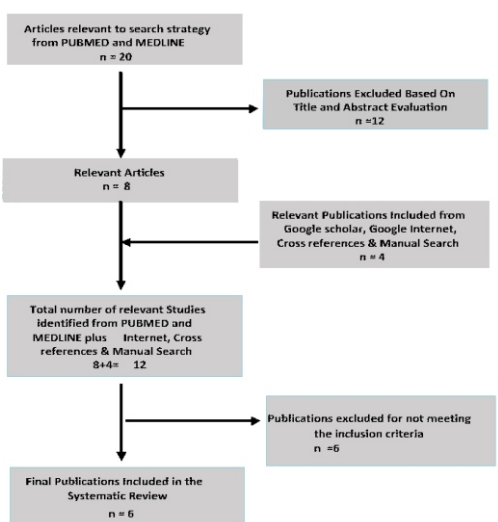

FIG.1. SEARCH FLOW CHART

RESULTS

Methods of Review:

The selection and exclusion of the reviewed studies are summarised in figure .1. The search strategy identified six studies that evaluate Human papilloma virus -6,16 in the pathogenesis of Oral lichen planus The description of the included studies is shown in table 1 and that of the excluded studies in table 2.

Included studies:

Out of the six included studies(21,22,23,24,25,26&27),detection of Human papilloma virus -16 was evaluated in all 6 studies and Human papilloma virus -6 was evaluated in 4 studies(21,22,23,25). Due to heterogeneity of the reviewed studies, a meta-analysis could not be performed. Yet a systematic review was conducted and the collected data were tabulated and analyzed.

TABLE 1.DESCRIPTION OF INCLUDED STUDIES

S.NO	AUTHOR	YEAR	SAMPLE SIZE	CONDITIONS ASSESSED FOR HPV	SUBTYPES ASSESSED	METHOD OF HPV DETECTION	STASTICAL ANALYSIS	HPV's DETECTED	RESULTS			LIMITATIONS
									HPV-6,16 subtypes	HPV others	p value	
1	Jontell M	1990	20-OLPe	OLPe	HPV-6,11,16,18	Southern blot hybridization and PCR	-	HPV-6,11,16,18	PCR;-HPV -6 in 5 OLP cases ,HPV-16 in 3 OLP cases	PCR;HPV -11 In 8 OLP cases SBH;HPV -11 In 8 OLP cases no other HPV detected by SBH	–	No statistical analysis done
2	Christiane Ostwald	2002	112-OSCC, 72-OL,12-Cheliti s,65-OLP	OSCC,OL,OLP,Chelitis	HPV-6,11,16,18	PCR/Southern Blot Hybridization	Chi-square test	HPV-16,18,6/11	HPV-16 positivity in 16 OL,35 OSCC,2 Cheilitis, 2 OLP.HPV -6/11 Positivity in 5-OSCC,8-OL,1-Cheilitis, 5-OLP 6	HPV -18 positivity in 16-OSCC,2-OL,4-OL	P value less than 0.005(significant)	Sample sizes vary between conditions
3	Giuseppina Campisi	2004	71 –OLP 68-OL	OL,OLP	HPV-6,16,18 31,33	PCR and sequencing analysis	Student t Test, Pearson chi Square test	HPV ,6,16, 18,31,33	HPV-16 In 2 OL,2 OLP. HPV -6 In 1 OLP	HPV -18 Positive in 9- OL,10-OLP HPV-31 in 1 OLP,HPV – 33 in 1 OL	P=0.005 (significant)	Failed to Demonstrate relationship between HPV infection and any specific clinical variant of OL and OLP

S.NO	AUTHOR	YEAR	SAMPLE SIZE	CONDITIONS ASSESSED FOR HPV	SUBTYPES ASSESSED	METHOD OF HPV DETECTION	STASTICAL ANALYSIS	HPV's DETECTED	RESULTS			Limitations
									HPV-6,16 subtypes	HPV others	p value	
4	Pratanporn Arirachakaran	2013	37-OLP	OLP	HPV -16	PCR	Phylogenetic tree cosstruction	HPV-16,33 ,6,11	HPV-16, In three OLP cases,HPV -6,In 2 OLP cases	HPV-33 In three OLP cases. HPV -11 in 2 OLPcases	–	Results were not configured well
5	Chetan .A.pol.	2015	60(30-normal, 30-OLP)	Oral lichen planus	HPV-16	Immunihistochemistry	Fisher's exact test	HPV-16	HPV -16 positivity in 21/30 OLP cases	–	P=0.0001(significant)	HPV evaluation done only by IHC
6	Mahnaz Sahebjamiee	2015	40-OLP and 40-normal(saliva and tissue)	OLP	HPV-16,18	PCR	Chi square and Fishers exact test	HPV 16,18	HPV-16 =8/40 OLP tissues ,3 saliva samples .5/40 healthy saliva positive for HPV-16	HPV-,18 =8/40 OLtissues ,3 saliva samples.	P=0.0367(Significant)	Done in spedific population .Not generalised.

TABLE 2.DESCRIPTION OF EXCLUDED STUDIES

	CITATION	REASONS FOR EXCLUSION
1	Paula Andrea Gabrielli Fregonesi, Debora Barreto Teresa(2003)	Study was not done in oral lichen planus
2	F. Elamin, H. Steingrimsdottir, S. Wanakulasuriya(1998)	Study was done in malignant lesions
3	Syrjanen SM, Syrjiincn KJ(1988)	Study was done in oral squamous cell carcinoma
4	Stina M. Syrjinen, Kari J. Syrjiinen (1986)	Study was done in oral squamous cell carcinoma
5	Mravak-Stipetić M1, Sabol I (2013)	Study was done in oral scrapings
6.	Jenice D'Costa a , Dhananjaya Saranatha (1998)	Study was done in OSCC

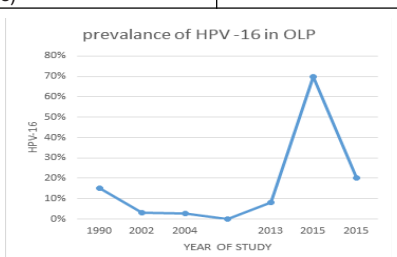

Figure 2

Table ;3

S.NO	AUTHOR	YEAR	HPV-16 positivecases
1	Jontell M	1990	(3)15%
2	Christiane Ostwald	2002	(2)3.10%
3	Giuseppina Campisi	2004	(2)2.80%
4	Pratanporn Arirachakaran	2013	(3)8.10%
5	Chetan .A.Pol	2015	(21)70%
6	Mahnaz Sahebjamiee	2015	(8)20%

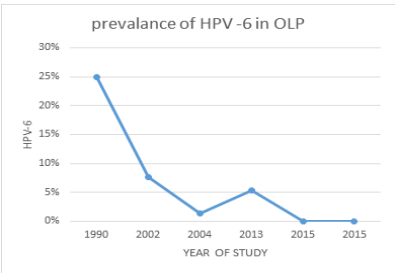

Figure 3

Table;4

S.NO	AUTHOR	YEAR	HPV-6 positive cases
1	Jontell M	1990	(5)25%
2	Christiane Ostwald	2002	(5)7.70%
3	Giuseppina Campisi	2004	(1)1.40%
4	Pratanporn Arirachakaran	2013	(2)5.40%

Discussion

Oral Lichen planus is a chronic inflammatory disease that affects the mucus membrane. Oral lichen planus (OLP), presents frequently in the fourth decade of life and affects women more than men in a ratio of 1.4:1[12]. The disease affects 1–2% of the population.It is seen clinically as reticular, papular, plaque-like, erosive, atrophic or bullous types. Intraorally, the buccal mucosa, tongue and the gingiva are commonly involved although other sites may be rarely affected.[13,14,15]

OLP is a chronic in ammatory disease in which the immunopathogenesis involves cell-mediated immune dysregulation. OLP is classi ed as a potentially malignant lesion of the oral mucosa with a malignant transformation rate of 0–6.25%[16]. Molecular and epidemiological studies suggest that HPV infection in the upper respiratory tract may play a role in the pathogenesis of head and neck tumours[17]. The role of HPV in premalignant lesions has also been studied[18,19].

HPVs are epitheliotropic DNA viruses with more than 150 genotypes. HPV classi cation has been based on the degree of HPV DNA homology. HPV has been detected in various types of oral benign and malignant lesions[20]. The etiology and pathogenesis of OLP has been the focus of much research.This along with the fact that HPV plays asignificant role in many oral beningn and malignant lesions has suggested a possible role of HPV in OLP This systematic review describing the role of human papilloma virus 6,16 in the pathogenesis of oral lichen planus,identified 6 studies involving 224 subjects of OLP investigated for presence of HPV – 16 and 4 studies with 154 subjects of OLP were investigated for the presence of HPV-6 .

Our data suggests that prevalence of HPV -16 in Oral lichen planus is increased over the past few years ,while that of HPV-6 has remained consistent . This could also be due to more studies that have investigated HPV -16 than HPV-6 in oral lichen planus

Jontell .M et al(21) in their study examined prevalence of HPV -6,16 in OLPe (erosive oral lichen planus) and found 15% HPV -16 and 25% HPV -6 and concluded that HPV may represent one of the risk factors in Oral lichen planus etiology ,along with carcinogens like tobacco and alcohol for oral squamous cell carcinoma in erosive oral lichen planus(21) . Christene ostwald et al (22)compared detection rates of HPV -6/11,16 and 18 between oral squamous cell carcinoma ,leukoplakia ,chelitis and oral lichen planus and found only 3.10% HPV- 16 and 7.70% HPV- 6 positivity and concluded that no association was seen between HPV and oral lichen planus.

Another study by Giuseppina et al(23),assessed the prevalence of HPV DNA in Oral leukoplakia and Oral lichen planus .In their study 2.8% HPV-16 and 1.40% HPV -6 positivity and the authors accomplish that no association seen between human papilloma virus and oral lichen planus. Chetan .A.Pol.(24) observed 70% HPV -16 positivity and established significant association between HPV -16 and oral lichen planus. Pratanporn Arirachakaran et al(25), did study on prevalence of HPV-6,16 in Thai patients .They noticed 8.10% HPV -16 and 5.40% HPV -6 posivity and they concluded that no prevalence of HPV-6,16 in Oral lichen planus patients.

Based on this systematic review it was evident that human papilloma virus (HPV)-6,16 does not seem to have role in the pathogenesis of oral lichen planus .

LIMITATIONS OF THE REVIEW:

We acknowledge the potential presence of publication bias might have occured within this review.

CONCLUSION:

From the studies included in the review, predominance for HPV-6,16 were not seen. Thereby this systematic review concludes that HPV-6,16 doesn't have role in the pathogenesis of Oral lichen planus.

CONFLICT OF INTEREST;
None declared.

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26.. Mahnaz Sahebjamiee, Lars Sand,1 Sharare Karimi,2 Jalil Momen Biettolahi,3 Fereshteh Jabalameli,3 and Jamshid Jalouli