Short thesis for the degree of doctor of phylosophy (Ph.D)

THE ENDOGENOUS AND EXOGENOUS RISK FACTORS OF ORAL PATHOLOGIC DISORDERS

By Ildikó Tar D.M.D.

Supervisor:
Ildikó Márton M.D., L.Ds., Ph.D.

UNIVERSITIY OF DEBRECEN
DOCTORAL SCHOOL OF DENTISTRY
DEBRECEN,2011.

1. INTRODUCTION

In our country the prevalence of oral disorders, like carious lesions, periodontal diseases, oral precancerotic lesions, and oral tumours is very high. In the north-eastern region oral condition of the population is the worst among all regions of Hungary. Neglected oral conditions increase the possibility of developing precancerotic lesions, among which the onset of leukoplakia and its subsequent malignization is the most probable. The relationship between precancerous lesions and other dental diseases is established by their infectious pathology and by their potential to maintain chronic inflammation in the surrounding mucosa. The irreversible destruction of hard dental tissues, caused by bacterial adherence, leading to the formation of sharp tooth edges and tartar deposition and subsequently mechanical irritation, helps the further colonization and multiplication of bacteria increasing the risk of precancerotic lesion and tumour formation.

The quality and quantity of bacteria, fungi, and viruses colonizing the oral cavity are affected by local and systemic factors. Regardless of periodontal disease, it is not totally clear that systemic factors can directly act on the development of other dental anomalies or in the pathogenesis of precancerotic disorders and tumour formation, or their effect is only exerted by microbiological factors or both.

2. AIMS

2.1. Relationship between selective IgA deficiency (SIgAD) an oral disorders.

1. What types of oral mucosal diseases do appear in patients with SIgAD?

2. Is oral lichen planus (OLP) among those mucosal disorders?

3. Which dental disorders (caries, periodontal disease) can be related to SIgAD?

Study design: case-control study.

2.2. Relationship between oral squamous cell carcinoma (OSCC) and the prevalence of human papilloma virus (HPV).

1. How much percentage of OLP, oral leukoplakia (OL), and OSCC lesions are affected by HPV?

2. What types of HPVDNA can be detected and in what copy numbers?

3. Is there a relationship between the HPVDNA statuses of certain patients' groups, their clinical, and pathological characteristics?

Study design: case-control study.

3. PATIENTS, MATERIALS, AND METHODS

3.1. RELATIONSHIPS BETWEEN ORAL DISORDERS AND SIGAD

3.1.1. INTRODUCTION CRITERIA OF SIGAD PATIENTS AND CONTROLS

In the February of 2004 34 patients (mean age±SD: 11.7±0.6 yr) with selective IgA deficiency were enrolled in this study. Admitted for regular dental check-up investigations to the Department of Pediatric Dentistry, MHSCUD in March and April of 2004, 113 healthy children (mean age±SD: 9.5±0.3 yr) were investigated as controls after finishing the screening of SIgAD patients. Salivary IgA was screened to exclude asymptomatic IgA deficiency and 2 controls were excluded because of low secretory IgA levels.

3.1.2. ORAL MUCOSAL, PERIODONTAL AND CARIOLOGICAL SCREENING.

On oral examination, to be performed by the study investigator (IT), mucous membrane lesions were registered and severity of periodontal disease and dental caries experience were assessed. Mucosal lesions presenting on oral examination or having been included in the paediatric immunology files of patients were registered. Because of the lack of a uniformly proper oral health history, mucosal lesions were not registered in controls.

The characterization of periodontal disease included full mouth periodontal measurements with the help of a periodontal probe: determination of plaque index (PlI), gingival index (GI), recession of gingiva and clinical periodontal pockets.

Carious lesions were detected with physical examination. In the lack of obvious approximal cavity formation bitewing radiographs were taken. Caries data were expressed according to the dmf-system. In the patient group, 7 children had primary, 20 mixed, and 7 permanent dentitions. In the control group, 11 children had primary, 67 mixed, and 33 permanent dentitions.

3.1.3. STATISTICAL ANALYSIS

None of the examined variables showed normal distribution characteristics. Comparison of data was performed with the Mann-Whitney test. P values below 0.05 were considered significant. Scores were expressed as mean ± SD values.

3.2. PRECANCEROUS LESIONS, OSCC, AND HPV

3.2.1. CHARACTERISTICS OF PATIENTS' GROUPS AND CONTROLS, INTRODUCTION CRITERIA

All specimens were collected between 2003 and 2007. Histopathological results were available at the time of sample collection in each case. Inclusion criteria for OSCC patients were i) being a newly diagnosed case and ii) not undergoing neoadjuvant chemo- or radiotherapy before the surgical intervention and sampling. Similarly, inclusion criteria for patients with potentially malignant oral lesions were i) being a newly diagnosed case and ii) not receiving any therapy for their lesion prior to sampling. All individuals fulfilling the inclusion criteria and agreeing to participate were enrolled.

Sixty-five patients with OSCC (51 male, 14 female; mean age 54.4; age 25-80), 44 patients with OL (14 male, 30 female; mean age 56.3; age 29-91) and 119 patients with OLP (31 male, 88 female; mean age 55.0; age 23-79) were enrolled. Fifty-eight of 119 OLP patients (16 male, 42 female; mean age 52.5; age 23-75) carried non-erosive/atrophic OLP (nonEA-OLP) lesion, whereas the other 61 OLP patients (15 male, 46 female; mean age 57.4; age 23-79) had erosive/atrophic OLP (EA-OLP) lesions. OLP lesions with mixed clinical presentation were classified as non-EA-OLP only if plaque and reticular areas were seen together; if atrophic or erosive areas were observed, the lesion was regarded as EA-OLP. Due to small size of the OL population, similar subgrouping was not applicable.

Controls were selected according to their age and healthy mucosa at our clinic's primary care ward. The 72 controls (19 male, 53 female, mean age; min-max: 52.0; 22-77) arrived from the same geographical region.

3.2.2. CYTOLOGICAL SAMPLING OF ORAL MUCOSA

In OL and OLP, exfoliated cells were collected from the surface of lesions. In all patient groups, prior to sampling of the lesion, exfoliated cells were harvested from apparently normal mucosa at the site farthest possible from the lesion. To avoid contamination of samples with saliva, sampling was preceded by two mouth rinses with physiological saline. Exfoliated buccal epithelial cells were collected from controls. Excised tissue specimens of OSCC patients were collected during surgical intervention from the centre of the tumour. Exfoliated cells were also collected from the tumour mass.

3.2.3. NESTED AND REAL TIME PCR FOR THE DETECTION AND GENOTYPING OF VIRAL DNA

DNA was isolated by TRI Reagent (Sigma-Aldrich, St. Louis, MO) according to the manufacturer's recommendation in case of tumour tissues. Exfoliated cells of OSCC, OL and OLP patients and controls were digested with proteinase K, treated with 5M NaCl after digestion and DNA was precipitated using 96% ethanol.

For detection and typing of HPVs, we used MY09/MY11-GP5+/GP6+ consensus nested PCR. HPV genotyping was performed using restriction fragment length polymorphism of MY or GP amplimers as described previously. PCR assays were performed twice using DNA from two independent DNA extraction processes. Identity of HPV 6, 11, 16, 18, 31 and 33 was confirmed by HPV E7 ORF specific PCR assays. Viral copy numbers were determined for lesion samples carrying 6, 11, 16, 18 and 33 by means of SYBR Green real-time PCR assays with the type-specific primers using

SYBR Green Master Mix (Applied Biosystems, Foster City, Ca, USA). All experiments were run in duplicates and repeated twice. Final copy numbers were calculated as the averages of the duplicate experiments and expressed as copy number in 1 μg total DNA. Samples with undetectable HPV in the real-time PCR (containing less than ten copies) were considered to contain ten copies for statistical purposes.

3.2.4. STATISTICAL ANALYSIS

Prevalence data were analyzed with chi-square and Fisher's exact tests. We calculated and compared virus copy number averages found in different patient groups using independent samples t-test. Association between patient data, HPV carriage and clinical appearance of diseases was evaluated by logistic regression.

4. RESULTS

4.1. RELATIONSHIP BETWEEN ORAL DISORDERS AND SIGAD

4.1.1. MUCOSAL DISORDERS

On oral examination of patients 1/34 (3%) leukoedema, 2/34 (6%) angular cheilitides and 3/34 (9%) geographic tongues were noted. Patients' history revealed 2/34 aphtous-like oral ulcers and 2/34 herpetic lesions: 1 herpetic gingivostomatitis and 1 labial herpetic lesion. Altogether 10/34 (29%) children with selective IgA deficiency were registered with oral mucosal lesions. Since oral health history of controls was incomplete, statistical comparison with respect to oral mucosal lesions among patients and controls was not performed.

4.1.2. PERIODONTAL CONDITION

PlI (0.87±0.46) and GI (0.53±0.34) of 32 patients and PlI (0.75±0.35) and GI (0.63±0.25) of 111 controls did not differ significantly. The individual findings varied considerably, ranging from some children with excellent oral hygiene and no gingivitis to some with high PlI scores and distinct gingivitis both among patients and controls. Neither patients nor controls presented either a pocket depth exceeding 3 mm, and/or recession of the gingiva, which excludes an advanced periodontal disease.

4.1.3. CARIOLOGICAL FINDINGS

Regarding caries experience, significant differences between patients and controls were observed both in combined dmft/dmfs and component dt and ds values. Differences in combined indices resulted from differences in the dt and ds components. The latter indices, representing decayed (d) teeth (t) and tooth surfaces (s) in the primary dentitions, were significantly higher in IgA deficient patients than in controls. No significant differences were found between patients and controls in respect of DMFT/DMFS indices and their components, characterizing permanent dentitions. Both groups included patients ranging from those who were cariesfree to those having high dmf/DMF scores.

4.2. RELATIONSHIP BETWEEN PRECANCEROTIC LESIONS AND HPV

4.2.1. HPV FREQUENCY IN DIFFERENT LESIONS

The HPV involvement of healthy mucosa in patients in HPV free lesions (3.6%) was equal with the HPV frequency of healthy controls (4.2%). Among controls **t**wo individuals were HPV16 positive, one individual carried HPV11.

As seen in the lesions, HPV carriage rates in the healthy also increased gradually. Regarding only patients with HPV positive lesions, HPV carriage rates were markedly higher in all patients groups compared to controls. Prevalence rates on the apparently healthy mucosa differed significantly from that found in healthy controls ($p<0.01$ in all comparisons), but not between groups ($p>0.05$). Prevalence in healthy mucosa of non-EA-OLP and EA-OLP patients did not differ.

The prevalence in OLP, OL and OSCC lesions increased gradually. All lesions carried HPV significantly more frequently than healthy controls ($p<0.001$ in all comparisons). Comparing different patient groups, HPV prevalence differed significantly only between OLP and OSCC patients ($p=0.047$).

Presence of HPV showed a strongly significant correlation with presence of all lesions compared to controls (OR (CI95%)=6.64 (1,79-24,63), 17.09 (4,84-60,38), 15.92 (4,33-59,59) and 20,97 (5,98-73,05) in non-EA-OLP, EA-OLP, OL and OSCC groups, respectively; $p<=0.005$ in all comparisons).

4.2.2. HPV GENOTYPES

Both high risk (16, 18, 31, 33, 39, 51) and low risk (6, 11, 32, 55, 57) genotypes appeared in the lesions. Genotypes were always low-risk types (1 HPV6 in OSCC, 1 HPV11 in OL and 3 HPV11s in OLP patients with HPV negative lesion). Genotypes of patients with HPV positive lesions were the same found in the lesion, excepting one HPV16 positive OSCC patient carrying HPV11 in the normal mucosa.

4.2.3. HPVDNA PREVALENCE RELATED TO CLINICAL AND PATHOLOGICAL CHARACTERISTICS

EA-OLP is associated with higher frequency of HPV carriage compared to non-EA-OLP (66.7% *vs*. 43.8%; OR=2.57, CI=1.16-5.72; p=0.021). Age and gender distribution of patients with high and low risk OLP was similar. HPV status and gender did not differ between OL patients with high and low risk lesions, but in patients younger than 50 years higher risk OL occurs more frequently than among older patients (50.0% *vs*. 21.4%; OR=3,67, CI=0,97-13,90), this correlation was not significant (p=0.056), however.

Averages of virus copy numbers were $5.2x10^2$ (range: 10-840), $6.8x10^3$ (range 10-51000), $7.2x10^3$ (range 10-27000) and $2.4x10^5$ (range 90-130000) per 1 µg total DNA in oral controls, in OLP, OL and OSCC patients, respectively. Copy number averages were significantly higher in all patient group than in the controls ($p<0.005$ in all comparisons). We did not find significant difference between OLP and OL patients, but both groups had copy numbers significantly lower than that found in OSCC (p=0.016 and p=0.019, respectively). When dividing OLP group into subgroups as above, copy numbers in non-EA-OLP and EA-OLP were comparable ($7.4x10^3$, range 10-51000 and $6.5x10^3$, range 10-24000, respectively; $p>0.05$). Interestingly, copy numbers in non-EA-OLP proved comparable to the copy numbers in the control population ($p>0.05$), but behaved similarly to undivided OLP in other comparisons. Comparisons of EA-OLP yielded results similar to comparisons of undivided OLP.

5. DISCUSSION

5.1. RELATIONSHIP BETWEEN ORAL LESIONS AND SIGAD

5.1.1. MUCOSAL DISEASES RELATED TO SIGAD

The frequency of oral mucosal lesions in children with selective IgA deficiency was low. The lesions were relatively mild and transient in nature. Neither pseudomembranous candidiasis nor lichen-like lesions were registered. Norhagen-Engström *et al*., investigating adults with selective IgA deficiency, reported on lichen like lesions. In contrast, Porter and Scully observed a much higher frequency of severe oral mucosal diseases, such as aphtae (61%), pseudomembranous candidiasis and herpetic lesions (25%). However, the latter patient population included disorders of cell-mediated immunity, in addition to IgA deficiency.

5.1.2. PERIODONTAL DISORDERS RELATED TO SIGAD

Periodontal condition of our patients was similar to controls, suggesting that selective IgA-deficiency did not alter the inflammatory host reaction to the periodontal microflora. This observation is similar to earlier results. Periodontal health varied between broad ranges both in patients and controls, which may be associated with wide inter-individual differences in oral hygiene.

5.1.3. CARIOLOGICAL FINDINGS RELATED TO SIGAD

Our study was the first to reveal a significant difference with respect to dental caries experience in primary dentition of children with selective IgA deficiency. Patients had significantly more decayed teeth (dt) and tooth

surfaces (ds) in their primary dentition than controls, resulting in significantly higher dmft and dmfs scores. Dental treatment activity was similar in the two groups as filled tooth/surface (ft/fs) indices did not differ significantly. Finding no differences in the permanent dentition of patients and controls can be explained by a shorter exposure time. Another study observed no difference in dental caries prevalence in adults with selective IgA deficiency than in matched controls. However, those investigators could not characterize decidous teeth. In conclusion, the present study showed that children with selective IgA deficiency are at risk for developing more dental caries than the healthy ones. The significance of higher caries frequency may result in an increase in retentive areas where plaque can be retained and cannot be removed by normal oral hygiene procedures. The teeth may also serve as a reservoir for respiratory pathogen colonization, a significant cause of morbidity in children with selective IgA deficiency.

5.2. HPV IN RELATIONSHIP WITH PRECANCEROUS LESIONS

5.2.1. HPV PREVALENCE IN LESIONS

In our study, prevalence pattern in different lesions was peculiar. In OLPs we found HPVs more frequently in EA-OLP than in nonerosive/nonatrophic lesions; erosive and/or atrophic lesions carried HPVs with similar frequency that found in OL. Thus, four prevalence rates were observed, i) control population, ii) non-EA-OLP, iii) EA-OLP and OL, and iv) OSCC. This is also reflected in prevalence on apparently healthy mucosa. This pattern is unlikely to be biased by differences in samples used, as in OSCC the sampling method is expected to underestimate HPV prevalence compared to using specimens of cells exfoliated from the tumour surface. Relatively few studies were

conducted in patient populations with oral potentially malignant disorders sufficiently large to draw firm conclusions; only two works, that of Campisi *et al.* (2004) and Ostwald *et al.* (2003) were based on histological characterization. Their prevalence rates were comparable to but lower than those found in our Eastern Hungarian population. Similarly to our data, Campisi *et al.* (2004) found significantly higher HPV carriage rates in patients with oral lesions compared to controls. As Ostwald *et al.* (2003) did not include a control population similar comparison to our data was not possible. Though there is possibility of false negative and false positive results, these are unlikely to bias the results presented. The PCR method used has excellent sensitivity (cca. ten copies), therefore this method is the best choice to avoid false negative results. Though the occurrence of false positives or cross-contamination can never entirely be ruled out, our data set is improbable to be biased by these, because i) all MY/GP nested assays were performed twice using two independent DNA extractions and ii) presence of HPV was confirmed by type-specific PCR (as well as real time PCR) assays for the most frequent mucosal genotypes. As HPVs unconfirmed by type-specific assays represent a very small proportion of the positives (0, 3, 2, 2 in controls, OLP, OL and OSCC patients, respectively), these could not alter the results profoundly even if some of them are false positives.

5.2.2. HPV GENOTYPES

Both low and high risk HPVs appeared in the lesions. Parallel the increase in malignant potential of lesions the frequency of high risk HPVs increased as well. HPVs carried in patients with HPV negative lesions were always low-risk types, while lesions harboured mostly high-risk HPVs.

5.2.3. HPVDNA PREVALENCE RELATED TO CLINICAL PARAMETERS AND PATHOLOGICAL CHARACTERISTICS

In the present study HPVDNA frequency was examined in association with clinical parameters like age, gender, and smoking habit. EA-OLPs associated with higher prevalence of HPV compared with non-EA-OLPs, but it has not showed any relationship with other clinical characteristics.

In the case of OL the non homogenous high risk type of it seems to appear more frequently in younger patients and it seems not to have any association with HPV. Previous studies could not show any relationship between HPV and lesion types. Though Campisi *et al* (2004) have investigated the possible effect of some clinical parameters on HPV prevalence in premalignant lesions, but they could not verify any factor to have an effect on HPV, except smoking.

Regarding copy numbers in oral lesions I could not make a comparison as there was no such study before. The progressive increase in HPV prevalence from lesions with low malignant potential to manifest cancer together with the high odds ratios may be explained in two ways. i) HPV plays a supplemental role in inducing and/or progression of potentially malignant lesions, or ii) lesions provide an environment increasingly favourable for HPVs as their malignant potential increases. In both cases presence of HPV may bear a prognostic significance. The first option is supported by finding high-risk HPVs consistently and low prevalence of low-risk HPV in lesions both in the present and in earlier studies. Another argument for the real aetiologic role is that patients HPV positive in the lesion carried HPVs in the apparently healthy mucosa more frequently than controls or patients with HPV negative lesions.

Patients with HPV negative lesions showed a HPV carriage rate in their healthy mucosa similar to that of controls. HPVs carried in patients with HPV negative lesions were always low-risk types, while lesions harboured mostly high-risk HPVs. Consequently, presence of HPVs on healthy mucosa seems to be a consequence of a HPV positive lesion.

Several types of cytogenetic and epigenetic alterations were found in the background of malignant transformation of OLP and OL, including loss of p53 function, enhancement of antiapoptotic processes and increased telomerase activity. These processes may be mediated by HPV E6 and/or E7 oncoproteins. Considering the HPV prevalence pattern found, it is tempting to hypothesize that HPVs may play some aetiologic role in malignant progression of oral potentially malignant disorders.

While it is obvious that HPVs alone are not capable of mediating malignant transformation of oral lesions, it is conceivable that they can enhance the effect of other carcinogens or agents provoking dysplasia. Our results suggest that the debate on the aetiological role of HPVs is probably worth to be extended to oral potentially malignant disorders, i.e. OLP and OL, as well.

6. SUMMARY

Oral disorders of children with SIgAD have never been investigated. The purpose of my study was to characterize these types of lesions. The only significant difference that I could find was in the case of their deciduous teeth. A significant difference was detected in their dmft and dmfs indices compared with healthy individuals.

In the other study the possible role of HPV was examined with the help of samples taken from premalignant lesions like OLP and OL, and tumours like

OSCC. Exfoliated cells were collected with the help of cytobrush. Further tests for the detection and genotyping of HPV were performed. HPV prevalence and virus copy numbers in lesions was significantly higher than on normal mucosa regardless of the sampling site. HPV detection rate and virus copy numbers increased parallel with the malignant potential of lesions. On the basis of previous findings it might be concluded that HPV might have a role in oral tumorigenezis, even from its initiation.

7. NEW FINDINGS

7.1. SELECTIVE IGA AND ORAL DISORDERS

1. It was showed that SIgAD is not related with any specific oral disorders.
2. There is no direct relationship between SIgAD and OLP.
3. Children with SIgAD have a higher risk to develop carious lesions in their deciduous teeth.

7.2. PRECANCEROUS LESIONS, ORAL SQUAMOUS CELL CARCINOMA AND HUMAN PAPILLOMA VIRUS

1. In this study the HPV detection rate is the highest among all studies.
2. Our results point out the importance of HPV carriage on healthy mucosa.
3. Our study was the first to publish copy numbers in OLP, OL, and OSCC.
4. In the case of OLP, OL and OSCC the association with HPV is not affected by smoking habits.

Register Number: DEENKÉTK /51/2011.
Item Number:
Subject: Ph.D. List of Publications

Candidate: Ildikó Tar
Neptun ID: BNNQ4J
Doctoral School: Doctoral School of Dental Sciences

List of publications related to the dissertation

1. **Tar I.**, Nemes É., Nemes J., Alberth M., Keszthelyi G.: A nyálimmunglobulinok (szekretoros IgA, IgM, IgG) mennyiségének és a cariesprevalencia közötti összefüggés vizsgálata deficienciákban (primer B-sejt).
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The Candidate's publication data submitted to the Publication Database of the University of Debrecen have been validated by Kenezy Life Sciences Library on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

01 June, 2011

Summarized impact factors of scientific articles used in the thesis: 5.059.
Impact factor of in extenso scientific articles: 17.381.