XEROSTOMIA AND ORAL MANIFESTATIONS OF SALIVARY GLAND DYSFUNCTION

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COURSE OBJECTIVES

• DEFINE AND DESCRIBE THE DIFFERENT CAUSES OF SALIVARY GLAND DYSFUNCTION
• DEFINE AND DESCRIBE HOW TO DIAGNOSE SALIVARY GLAND DYSFUNCTION
• DEFINE AND DESCRIBE ORAL MANIFESTATIONS OF SALIVARY GLAND DYSFUNCTION
• DESCRIBE EVIDENCE-BASED MANAGEMENT STRATEGIES FOR SALIVARY GLAND DYSFUNCTION

PRODUCTION OF SALIVA

• HEALTHY ADULT PRODUCES 1.5 L OF SALIVA IN 24 HOURS.
• 3 MAJOR PAIRS OF SALIVARY GLANDS
  • PAROTID
  • SUBMANDIBULAR
  • SUBLINGUAL
• MINOR SALIVARY GLANDS
  • APPROXIMATELY 750
  • NOT LOCATED IN THE GINGIVA OR ANTERIOR HARD PALATE
PRODUCTION OF SALIVA

• PERCENTAGE OF SALIVA PRODUCTION
  • PAROTID 45%
  • SUBMANDIBULAR 45%
  • SUBLINGUAL 5%
  • MINOR SALIVARY GLANDS 5%

• THE SUBLINGUAL AND MINOR SALIVARY GLANDS PRODUCE THE MAJORITY OF MUCOUS SECRETIONS

• SALIVARY DYSFUNCTION
  • UWS: <1.5 ML IN 15 MIN
  • SWS: <10.5 ML IN 15 MIN

SALIVARY GLAND PHYSIOLOGY

• ACINAR CELLS INITIALLY SECRETE AN ISOTONIC FLUID (140 MEQ/L NaCl)
  • CONTAINS 85% OF THE EXOCRINE SALIVARY PROTEINS

• AS SALIVA PASSES THROUGH DUCTAL TISSUE GET REABSORPTION OF NaCl
  • RESULTS IN A HYPOTONIC (30 MEQ/L NaCl) SALIVA
  • DUCTAL CELLS CONTRIBUTE 15% OF REMAINING SALIVARY PROTEINS
SALIVARY GLAND PHYSIOLOGY

• AUTONOMIC CONTROL OF SECRETION
  • PARASYMPATHETIC STIMULATION RESPONSIBLE FOR SECRETORY FUNCTION
  • SYMPATHETIC STIMULATION RESPONSIBLE FOR PROTEIN SECRETION
  • IF BLOCK PARASYMPATHETIC INNERVATION, GLANDULAR ATROPHY OCCURS
  • BLOCKING SYMPATHETIC INNERVATION HAS LITTLE EFFECT ON THE GLANDS

CAUSES OF HYPOSALIVATION

• PROPOSED MECHANISMS FOR HYPOSALIVATION INCLUDE:
  • NEUROTRANSMITTER RECEPTOR DYSFUNCTIONS
  • SALIVARY GLAND PARENCHYMAL DESTRUCTION
  • RADIATION-INDUCED CELLULAR DNA DAMAGE
  • IMMUNE DYSREGULATION THAT MAY INTERFERE WITH SECRETORY PROCESSES
  • ALTERATIONS OF FLUID AND ELECTROLYTES (DEHYDRATION)
  • COMBINATIONS OF THE ABOVE

MEDICATION-INDUCED XEROSTOMIA

• >1500 MEDICATIONS HAVE BEEN IMPLICATED AS CAUSING XEROSTOMIA
• 80% OF THE MOST COMMONLY PRESCRIBED MEDICATIONS HAVE BEEN REPORTED TO CAUSE XEROSTOMIA.
• XEROSTOMIC DRUGS CAN BE FOUND IN 42 DRUG CATEGORIES AND 56 SUB-CATEGORIES
• MED USE INCREASES WITH AGE
  • > 75% OF PERSONS AGED ≥ 65 TAKING AT LEAST ONE PRESCRIPTION MEDICATION
**MEDICATION-INDUCED XEROSTOMIA**

- Drugs commonly associated with dry mouth drugs which directly damage salivary glands:
  - Anti-hyperplastic agents

- Drugs with anticholinergic activity:
  - Agents such as atropine and scopolamine
  - Antihypertensives, e.g. propranolol
  - Numbness and dry mouth
  - Selective serotonin-reuptake inhibitors
  - Phenothiazines
  - Benzodiazepines
  - Opiates
  - Antihistamines

- Drugs acting on sympathetic system:
  - Drugs with sympathetic activity (e.g., ephedrine)
  - Inadrenergic-receptor agonists and alpha antagonists (e.g., clonidine)
  - Beta blockers (e.g., atenolol, propranolol) also change salivary protein levels.

- Drugs which deplete fluid:
  - Opioids

**MEDICATION IMPACT ON SALIVARY FLOW**

Multicenter retrospective exploratory study

US Site: Carolinas Center for Oral Health, Charlotte, NC (current data)

Other sites: Copenhagen, Netherlands (X2), Croatia, Spain

Time frame: January 01, 2010 - May 31, 2014

973 Patients

61 Eligible

Research Objectives

- Determine the overall effects of the medications on unstimulated and stimulated salivary flow
  - Number of medications
  - Classes of medications
  - Single medications
- Determine the effects of medication on unstimulated and stimulated salivary flow specifically in the Sjögren's syndrome population
- Analyze the effects of concurrent systemic diseases on unstimulated and stimulated salivary flow in both subgroups (non-SS patients/SS patients)
RESEARCH METHODOLOGY

- Head and neck examination including the dental and oral mucosal condition on all study participants
- Saliva was collected in a standardized manner as unstimulated whole saliva (UWS) and stimulated whole saliva (SWS)
- All concurrent medications were collected by a questionnaire completed at the time of the dental visit by the patient
- Demographics, systemic diseases, vital signs and social history were collected

<table>
<thead>
<tr>
<th>Table 1: Baseline characteristics separated for all three groups (all patients, non-Sjögren’s Syndrome, and Sjögren’s Syndrome patients).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Categories</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Patients (%)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Male (%)</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>UWS (ml/15min)</td>
</tr>
<tr>
<td>SWS (ml/15min)</td>
</tr>
<tr>
<td>Right Schirmer’s Test (mm/min)</td>
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<tr>
<td>Left Schirmer’s Test (mm/min)</td>
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<tr>
<td>Total Schirmer’s Test (mm/min)</td>
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<tr>
<td>Total Concurrent Diseases</td>
</tr>
<tr>
<td>Systolic Blood Pressure (SBP) (mmHg)</td>
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<tr>
<td>Diastolic Blood Pressure (DBP) (mmHg)</td>
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<tr>
<td>Heart Rate (HR) (beats/min)</td>
</tr>
<tr>
<td>Tobacco Users</td>
</tr>
<tr>
<td>Alcohol Users</td>
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<tr>
<td>Stil Drug Users</td>
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</tbody>
</table>

Figure: Graph representing salivary flow as number of medications. The regression line for unstimulated salivary flow is illustrated in blue. The regression line for stimulated salivary flow is illustrated in orange.
RESEARCH CONCLUSIONS IN DRY MOUTH, NON-SS PATIENTS:

- Both unstimulated and stimulated salivary flow rapidly approach zero as number of medications increase.
- The results of this study suggest that users of multiple medications are at increased risk for dry mouth.
- Although the population is biased towards non-Sjögren’s Syndrome patients complaining of xerostomia, the results are generalizable to patients not complaining of xerostomia.
- Medications targeting the nervous system (including anesthetics, analgesics, antiepileptics, anti-Parkinson drugs, psycholeptics, and psychoanaleptics) have a significantly lower salivary flow (both UWS and SWS) than users not taking these medications.
- Users of hormonal preparations, excluding sex hormones and insulin, have a significantly lower unstimulated salivary flow than non-users. This includes pituitary and hypothalamic hormones, corticosteroids, pancreatic hormones, and hormones for calcium homeostasis, very common in the general population.
- Based on the results of this study, both unstimulated and stimulated salivary flow decreases as number of concurrent systemic diseases increase. Those patients with an increased number of diseases are at a higher risk for dry mouth.

RESEARCH CONCLUSIONS IN SS PATIENTS:

- This is the first study that analyzes both medication and concurrent systemic diseases’ effects on both unstimulated and stimulated salivary flow in a population of SS patients.
- This study concludes that both unstimulated and stimulated salivary flow rapidly approach zero as number of medications increase, which is not consistent with previous findings with SS patients.
- This could be due to an increased sample size, or by a skewed study population who use a higher number of medications.
- Users of hormonal preparations, a category of medication not previously explored with SS patients, have a significantly lower unstimulated salivary flow than non-users.
- No other categories were found to have a significant effect in the SS population.
- Concurrent systemic diseases have no significant effects on salivary flow in the SS population.
RADIATION THERAPY

• EXTERNAL BEAM RADIATION THERAPY (HEAD AND NECK, MANTLE, WHOLE BODY)
  • CONVENTIONAL RT
  • IMRT
  • 3D-CRT

• RADIOIODINE THERAPY (131I)

Jensen SB et al. J Supp Care CA. 2010. 18(8)
RADIOACTIVE IODINE THERAPY

• THE WEIGHTED PREVALENCE OF XEROSTOMIA
  • 0.5% (0.7-7.7) BEFORE TREATMENT
  • 33.6% (0-75) - 37.8% (15.8-59.8) AT 1-2 YEARS AFTER TREATMENT

• SALIVARY FLOW
  • REDUCED BY 27%-41% AND 27%-36% FOUR MONTHS TO 20 YEARS AFTER RADIOACTIVE IODINE TREATMENT.
  • ANOTHER STUDY FOUND NO DIFFERENCE AT 8 YEARS POST-TX.

SJÖGREN'S SYNDROME (VS. DISEASE)

• SS IS AN AUTOIMMUNE EXOCRINOPATHY, CHARACTERIZED BY DRYNESS OF THE MOUTH AND EYES RESULTING FROM A CHRONIC, PROGRESSIVE LOSS OF SECRETORY FUNCTION.
• PREVALENCE: 2-4 MILLION IN US
• SS IS THE SECOND MOST COMMON RHEUMATIC DISEASE
SJÖGREN’S SYNDROME IS A SYSTEMIC DISORDER

• PRIMARY SS: SALIVARY AND LACRIMAL INVOLVEMENT
• SECONDARY SS: SALIVARY AND/OR LACRIMAL INVOLVEMENT PLUS ANOTHER CONNECTIVE TISSUE DISEASE
  • RHEUMATOID ARTHRITIS
  • SYSTEMIC LUPUS ERYTHEMATOSUS
  • SCLERODERMA

SJÖGREN’S SYNDROME

• F > M (9:1)
• AGE: MID 50’S
• INCREASED RISK OF DEVELOPING LYMPHOMA

REVISED INTERNATIONAL CRITERIA FOR SJÖGREN’S SYNDROME

I. OCULAR SYMPTOMS
II. ORAL SYMPTOMS
III. OCULAR SIGNS
IV. HISTOPATHOLOGY
V. SALIVARY GLAND INVOLVEMENT
VI. AUTOANTIBODIES

*EXCLUSIONS: H/O HEAD & NECK, HIV, GVHD, PRE-EXISTING LYMPHOMA, USE OF ANTI-CHOLINERGIC DRUGS
REVISED INTERNATIONAL CRITERIA FOR SJÖGREN'S SYNDROME

I. OCULAR SYMPTOMS
1. DAILY, PERSISTENT, TROUBLESOME DRY EYES FOR >3 MONTHS?
2. RECURRENT SENSATION OF SAND OR GRAVEL IN EYES?
3. USE TEAR SUBSTITUTES >3 TIMES A DAY?

II. ORAL SYMPTOMS:
1. DAILY FEELING OF DRY MOUTH FOR >3 MONTHS?
2. RECURRENT OR PERSISTENT SWOLLEN SALIVARY GLANDS?
3. FREQUENTLY DRINK LIQUIDS TO EASE SWALLOWING?
AUTOANTIBODIES

- Anti-SS-A and Anti-SS-B
- First found using experiments with SS sera and a salivary gland extract
- Produced in very high amounts
- Made by circulating lymphocytes and lymphocytes that have infiltrated the salivary glands

OTHER SEROLOGIC FINDINGS IN SJÖGREN'S SYNDROME

- Very elevated serum immunoglobulins; polyclonal activation of B cells; spontaneous secretion of antibodies
- Rheumatoid factors
- Several inflammatory proteins (C-reactive protein)
- Anti-cardiolipin antibodies and other autoantibodies
LYMPHOMA AND SS

- 44-FOLD INCREASED RISK OF LYMPHOMA IN PRIMARY SS
  - SG OR EXTRA-SG (80% MALT TYPE)
- META ANALYSIS ZINTZARAS, 2005
  - THE 20 STUDIES CHOSEN FOR THE ANALYSIS INCLUDED 6 FOR SLE, 9 FOR RA, AND 5 FOR PSS.
  - HIGH RISK OF NHL DEVELOPMENT FOR PSS (RANDOM EFFECTS SIR, 18.8; 95% CONFIDENCE INTERVAL [CI], 9.5-37.3).
  - MODERATE RISK FOR SLE (RANDOM EFFECTS SIR, 7.4; 95% CI, 3.3-17.0).
  - LOWER RISK FOR RA (RANDOM EFFECTS SIR, 3.9; 95% CI, 2.5-5.9).

IN RA, THE RANDOM EFFECTS SIRS OF NHL WITH CONVENTIONAL ANTIRHEUMATIC TREATMENT, CYTOTOXIC TREATMENT, AND TREATMENT WITH A BIOLOGICAL AGENT WERE 2.5 (95% CI, 0.7-9.0), 5.1 (95% CI, 0.9-28.6), AND 11.5 (95% CI, 3.7-26.9), RESPECTIVELY.
EXTRAGLANDULAR MANIFESTATIONS

- Dryness of other mucous membranes
- Inflammation of other organ systems (digestive system, kidneys, liver, lungs, thyroid, nervous system, BVS)
- Signs/symptoms
  - Fatigue
  - Muscle and joint pain
  - Nausea
  - Difficulty swallowing
  - Heartburn
  - Cough
  - Numbness and tingling of extremities
  - Muscle weakness

The end results of the pathologic process in the salivary glands in Sjögren's syndrome are reduction in functional acinar tissue, a loss of secretory output, and symptoms of oral dryness.
FUNCTION OF SALIVA

TEETH

- Buffer
- Protect from demineralization
- Remineralization
- Lubrication

- Bicarbonate
- Phosphate
- Proteins
- Mucins
- Ca$^{2+}$
- Phosphate
- PRPs
- Statherin
- Mucins
- PRGs

FUNCTION OF SALIVA

FOOD

- Bolus formation
- Taste
- Digestion

- Mucins
- Water
- Gustin
- Zn$^{2+}$
- Water
- Amylase
- Protease
- Lipase
- DNAse
- RNAase

FUNCTION OF SALIVA

Microorganisms

- Anti-Viral
- Anti-Fungal
- Anti-Bacterial
- Cystatin
- Histatins
- Chromagranin A
- Immunoglobulin
- SLPI
- Cystatins
- Histatins
- VEGF
- SLPI
- Lysozyme
- Lactoferrin
- Calprotectin
- Lactoperoxidase
- Immunoglobulin
- Chromagranin A
CLINICAL FEATURES OF SALIVARY GLAND HYPOFUNCTION IN SJÖGREN’S SYNDROME

• ORAL HARD AND SOFT TISSUE SIGNS
• SALIVARY SIGNS
• OTHER SIGNS
SOFT TISSUE EFFECTS OF SALIVARY DYSFUNCTION IN SJÖGREN'S SYNDROME

• MUCOSAL DRYNESS AND ATROPHY
• INCREASED INFECTIONS
  • FUNGAL, BACTERIAL
• LOSS OF PAPILLATION OR FURROWING OF TONGUE
SALIVARY SIGNS OF SALIVARY DYSFUNCTION

• DIMINISHED SECRETIONS ON PALPATION
• THICKER, OPAQUE, OR VISCOUS SECRETIONS
• RECURRENT SALIVARY GLAND INFECTION
• ENLARGED SALIVARY GLANDS
OTHER CLINICAL FEATURES OF SALIVARY GLAND HYPOFUNCTION

• DIFFICULTIES CHEWING, SWALLOWING AND SPEAKING
• ALTERED OR DIMINISHED TASTE ACUITY
• COMPROMISED NUTRITION
• BURNING SENSATION

SYMPTOMS OF SALIVARY HYPOFUNCTION

• DRYNESS WHEN EATING MEALS
• DIFFICULTY SWALLOWING DRY FOODS
• A NEED TO DRINK FLUIDS WHEN SWALLOWING DRY FOODS
• THE IMPRESSION OF TOO LITTLE SALIVA

ORAL BURNING

• MANY LOCAL OR SYSTEMIC CONDITIONS MAY BE THE UNDERLYING CAUSE
  • TISSUE TRAUMA FROM DECREASED SALIVA LUBRICATION
  • PARAFUNCTIONAL HABITS
  • CANDIDIASIS
  • HEMATINIC DEFICIENCY
  • UNCONTROLLED DIABETES?
  • CNS LESION
  • CONTACT SENSITIVITY/ALLERGY
  • VESICULOSITISING DISEASE (LP, PEMPHIGOID, PEMPHIGUS)
• BURNING MOUTH SYNDROME (BMS): DIAGNOSIS OF ELIMINATION
BURNING MOUTH SYNDROME

• The cause of BMS is unknown—related to a neuropathy.
• More common perimenopausal women
• Management
  • Alpha lipoic acid 300 mg 2x/day
  • Benzodiazepines: clonazepam (0.25 - 0.5 mg)
  • Gabapentin (100-1800 mg)

XEROSTOMIA AND ORAL BURNING

• A retrospective cohort study of patients with a complaint of dry mouth.
• Dictation notes and charts of patients meeting these criteria from January 2004 to June 2009.
• 952 new patient encounters were examined and 170 met the inclusion criteria.
  • Yes to at least one of the following questions: “Have you had a daily feeling of dry mouth for more than 3 months?” or “Do you frequently drink liquids to aid in swallowing dry foods?”
  • Unstimulated and stimulated saliva flow
  • Work up for Sjögren’s syndrome when appropriate

XEROSTOMIA AND ORAL BURNING

• What is the prevalence of oral burning in patients with a complaint of dry mouth?
• What predicts the presence of a burning in dry mouth patients?
Univariate analysis of dry mouth patients with and without complaints of oral burning.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Negative oral burning</th>
<th>Positive oral burning</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number (%)</td>
<td>170</td>
<td>102 (60.0)</td>
<td>68 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>17 (10)</td>
<td>13 (12.8)</td>
<td>4 (5.9)</td>
<td>0.1940</td>
</tr>
<tr>
<td>Female (%)</td>
<td>153 (90)</td>
<td>89 (87.3)</td>
<td>64 (94.1)</td>
<td></td>
</tr>
<tr>
<td>Mean age (range)</td>
<td>58.0 (25-89)</td>
<td>56.2 (28-89)</td>
<td>61.1 (25-89)</td>
<td>0.0213</td>
</tr>
<tr>
<td>Stimulated salivary flow; mean ml/15min. (range)</td>
<td>10.43 (0-50.7)</td>
<td>11.2 (0-50.7)</td>
<td>9.3 (0-37.4)</td>
<td>0.2450</td>
</tr>
<tr>
<td>Insomnia medication (%)</td>
<td>31 (18)</td>
<td>15 (14.7)</td>
<td>16 (23.5)</td>
<td>0.1444</td>
</tr>
<tr>
<td>NSAID (%)</td>
<td>37 (22)</td>
<td>27 (26.5)</td>
<td>10 (14.7)</td>
<td>0.0686</td>
</tr>
<tr>
<td>Herbal medication (%)</td>
<td>88 (52)</td>
<td>60 (58.8)</td>
<td>28 (41.2)</td>
<td>0.0241</td>
</tr>
<tr>
<td>Taste disturbances (%)</td>
<td>28 (16)</td>
<td>13 (12.8)</td>
<td>15 (22.1)</td>
<td>0.1087</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>12 (7)</td>
<td>8 (7.8)</td>
<td>4 (5.9)</td>
<td>0.7645</td>
</tr>
<tr>
<td>Removable prosthesis (%)</td>
<td>19 (11)</td>
<td>6 (5.9)</td>
<td>13 (19.1)</td>
<td>0.0073</td>
</tr>
</tbody>
</table>

**XEROSTOMIA AND ORAL BURNING**

- Evaluated the following in multivariate analysis: age, gender, current smoking, removable prostheses, Sjögren's Syndrome, stimulated saliva, taste disturbance, and herbal medication.
- Age (OR 1.03; CI 1.00-1.05, P=0.028) and use of herbal medications (OR 0.26; CI 0.10-0.67, P=0.005) were found to be significant.

- Some of herbal medications may be protective against burning.
- It is also possible that herbal medications are not protective, but rather their use may be an alternative for xerostomic prescription medications that can precipitate a feeling of burning mouth.
- Fifty one (30%) had Sjögren's Syndrome (SS)
  - 39 Primary SS and 12 Secondary SS.
  - Oral burning was identified in 23 (45%) of all SS patients.
TREATMENT IMPLICATIONS

• POINT TO NEW BIOLOGICAL PATHWAYS
• DISCOVER IF GENETIC ALTERATIONS INCREASES RISK OF SS
  • POLYMORPHISMS [SNP]
• POTENTIAL TO IDENTIFY NEW THERAPEUTIC TARGETS
HORMONE DYSREGULATION

- Female:Male is 9:1
- Perimenopausal
- Clinical trial with DHEA
  - Benefit in one trial
  - DHEA is a precursor to androgens

DHEA is a precursor to androgens

- 36 patients DHEA vs. placebo
  - No difference in study outcomes

Forsblad-D'Elia et al. Low serum levels of sex steroids are associated with disease characteristics in primary Sjogren's Syndrome; supplementation with Dehydroepiandrosterone restores the concentrations. J Clin Endocrinol Metab. 2009 Jun;94(6):2044-51.

Virkki et al. Arth Care Res. 2010
- Enrolled 107 PSS with more severe fatigue and DHEAS values below the mean.
- 50 mg DHEA did not help fatigue better than placebo
**Hypothetical Pathogenesis**

- Genetics
- Environment
- Cytokines
- Antibody production
- Lymphocyte migration into glands
- Salivary/Lacrimal glands
- Apoptosis
- SS-A, SS-B (anti-SSA/SSB)
- Autonomic (M3 mAchR)
- Parasymp.
- Hormone dysregulation
- Cell adhesion molecules
- BAFF
- Anti-TNF-α
- Inflammatory cytokine demonstrated in SS
- New therapies to block TNF-alpha are beneficial for RA

### Clinical Manifestations

- **SS-A, SS-B (anti-SSA/SSB)**
- **Anti-TNF-α**
- **Clinical trial of Etanercept in SS**
  - 36 patients: Etanercept vs. placebo
  - Minimal benefit in study outcomes
- **Multicenter trial of Infliximab**
  - 103 patients: Infliximab vs. placebo
  - No benefit in study outcomes

*References:*

### Anti-TNFα

- **Clinical trial of Thalidomide in SS**
  - Stopped early due too many adverse events from the medication
- **Significant changes in markers of cell activation found in treated patients**

*References:*
Hypothetical Pathogenesis

Genetics → Salivary/Lacrimal Glands → Lymphocyte Migration into Glands → Antibody production

- Cytokines
- BAFF (B CELL ACTIVATING FACTOR)
  - REQUIRED FOR B CELL GROWTH AND MAINTENANCE
  - DEFICIENCY IN BAFF DECREASES B CELLS AND ANTIBODY RESPONSE
  - BAFF OVEREXPRESSION LINKED TO AUTOIMMUNE DISEASE
- SS VS. CONTROLS
  - ↑ SERUM BAFF
  - ↑ TISSUE BAFF
  - BAFF HIGHER IN SS THAN SLE AND RA

TREATMENT IMPLICATIONS

- RITUXIMAB
  - DASS S ET AL REDUCTION OF FATIGUE IN SJÖGREN SYNDROME WITH RITUXIMAB: RESULTS OF A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY ANN RHEUM DIS. 2008 NOV67(11):1541-4
RITUXIMAB

• MEIJER ET AL. ARTH RHEUM. 2010
  • 30 PSS PATIENTS (2:1 ACTIVE:PLACEBO)
  • SIGNIFICANT INCREASE STIMULATED WHOLE SALIVARY FLOW
  • DECREASE IN B CELL AND RF LEVELS

TREATMENT IMPLICATIONS

• POTENTIAL THERAPY
• LARGER RCT TO CONFIRM
• CANDIDATES FOR B CELL DEPLETION THERAPY?
  • NEW ONSET VS. MORE PRONOUNCED EXTRAGLANDULAR DISEASE

Hypothetical Pathogenesis

Genetics  Environment  Salivary/Lacrimal Glands  Lymphocyte Migration into Glands  Cell Adhesion Mol

Cytokines  Antibody production  SS-A, SS-B Antinuclear (Sjögren's-like)  Apoptosis  Purification  Clinical Manifestations

Dysregulation  BAFF
AUTONOMIC DYSFUNCTION

• FDA APPROVED MEDICATIONS FOR DRY MOUTH
  • CEVIMELINE (EVOXAC®) 30 MG TID
  • PILOCARPINE (SALAGEN®) 5 (17.5) MG QID
• CLINICAL TRIALS HAVE SHOWN A SIMILAR BENEFIT FOR DRY EYES.

SIDE EFFECTS ARE COMMON WITH BOTH PILOCARPINE AND CEVIMELINE DUE TO WIDESPREAD EXOCRINE STIMULATION.

SWEATING
FLUSHING
URINARY URGENCY
GI UPSET

ORAL DRYNESS

• SALIWELL DEVICE: ELECTROSTIMULATION OF NERVES THAT CONTROL SALIVA
• IMPROVEMENT IN DRYNESS

http://www.saliwell.com
HYPNOSIS

- 55 randomized to 3 sessions
  - Sham placebo
  - Hypnosis

- Primary outcome was improvement in report of oral dryness: VAS 0-100 (dry as a desert)
  - Sham placebo:
    - Baseline - 77
    - Visit 6 - 87
  - Hypnosis:
    - Baseline - 73
    - Visit 6 - 59

Salivary gland hypofunction and xerostomia

MANAGEMENT

- The panel recommends the use of parotid-sparing HAT for prevention of salivary gland hypofunction and xerostomia in head and neck cancer patients (Level of Evidence II, Recommendation Grade A).
- No guidelines possible for use of amifostine to prevent xerostomia during RT for head and neck cancer due to lack of consensus on the interpretation of existing evidence (Level of Evidence II, Recommendation Grade C).
- The panel recommends the use of oral pilocarpine following radiation therapy in head and neck cancer patients for improvement of xerostomia; the improvement of salivary gland hypofunction (Level of Evidence II, Recommendation Grade B).
- The panel cannot recommend the use of oral pilocarpine during radiation therapy in head and neck cancer patients for improvement of xerostomia as the results of the various randomized clinical trials were equivocal (Level of Evidence II, Recommendation Grade C).

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Salivary gland hypofunction and xerostomia

• MANAGEMENT

• NO GUIDELINE POSSIBLE FOR USE OF GUSTATORY AND MASTICATORY STIMULATION DUE TO LITTLE EVIDENCE ON WHICH TO BASE A GUIDELINE SINCE THIS HAS BEEN SPARSELY ADDRESSED SPECIFICALLY FOR PATIENTS SUFFERING FROM XEROSTOMIA INDUCED BY CANCER THERAPIES (LEVEL OF EVIDENCE III, RECOMMENDATION GRADE D).

• THE PANEL RECOMMENDS THE USE OF ORAL MUCOSAL LUBRICANTS/SALIVA SUBSTITUTES FOR SHORT-TERM IMPROVEMENT OF XEROSTOMIA FOLLOWING RADIATION THERAPY IN HEAD AND NECK CANCER PATIENTS (LEVEL OF EVIDENCE II, RECOMMENDATION GRADE B).

• THE PANEL SUGGESTS THAT THE OBTAINED LEVEL OF SPARING BY SUBMANDIBULAR SALIVARY GLAND TRANSFER MIGHT BE OF CLINICAL SIGNIFICANCE (LEVEL OF EVIDENCE IV, RECOMMENDATION GRADE B).

• THE PANEL SUGGESTS THE USE OF ACUPUNCTURE TO STIMULATE SALIVARY GLAND SECRETION AND TO ALLEVIATE XEROSTOMIA (LEVEL OF EVIDENCE II, RECOMMENDATION GRADE C).

• NO GUIDELINE POSSIBLE FOR HYPERBARIC OXYGEN TREATMENT OF XEROSTOMIA DUE TO NO EVIDENCE ON WHICH TO BASE A GUIDELINE (LEVEL OF EVIDENCE IV, RECOMMENDATION GRADE D).

Hypothetical Pathogenesis

PALLIATION

• WATER
• WATER
• WATER
PALLIATION

• INCREASED HUMIDITY
• ORAL RINSES
• HYDRATING EMOLLIENTS

MANAGEMENT APPROACHES: HARD TISSUES

• FLUORIDE (OTC VS. PRESCRIPTION)
• LIMIT SUGAR INTAKE
• ORAL HYGIENE
• FREQUENT DENTAL VISITS
• CHLORHEXIDINE
• XYLITOL ARTIFICIAL SWEETENER

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MANAGEMENT APPROACHES: SOFT TISSUES

• ANTI-FUNGALS
• BURNING SENSATION
  • HEMATINIC DEFICIENCY (TX: REPLACEMENT)
  • FUNGAL (TX: ANTI-FUNGALS)
  • BURNING MOUTH SYNDROME (TX: MEDS)

MANAGEMENT APPROACHES: ORAL DRYNESS

• WATER
• INCREASED HUMIDITY
• ARTIFICIAL SALIVA
• HYDRATING EMOLLIENTS
• SUGAR FREE CHEWING GUM OR MINTS
• ACUPUNCTURE
A COMBINATION OF THESE APPROACHES IS OFTEN NECESSARY FOR SUCCESSFUL MANAGEMENT OF XEROSTOMIA AND THE ORAL MANIFESTATIONS FROM SALIVARY DYSFUNCTION

QUESTIONS?

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