Objectives

By the end of the lecture the students will:
- Learn definition and details of common syndromes of the head and neck associated with oral soft tissue lesions
- Be able to give clinical differential diagnosis of oral soft tissue lesions with regard to syndromic associate

Syndrome

- In medicine and psychology, syndrome is the collection of signs and symptoms that are observed in, and characteristic of, a single condition.
- In medical genetics, syndrome refers specifically to medical condition where the underlying genetic cause has been identified, and the collection of symptoms is pathogenetically related.

Contents

- Down syndrome
- Syndrome associated with gingival fibromatosis
- Papillon-Lefèvre Syndrome
- Haim-Munk syndrome
- Ramsay Hunt syndrome
- Behçet’s Syndrome
- Melkersson-Rosenthal syndrome
- Syndrome associated with pigmentation
- Peutz-Jegher syndrome
- Neurofibromatosis I, II
- Multiple endocrine neoplasia
- Ehlers-Danlos Syndrome
- Tuberous sclerosis
- Multiple hamartoma syndrome
- Plummer-Vinson syndrome
- Burning mouth syndrome
- Sjögren’s syndrome
- Frey syndrome
- Syndrome and cancer

Down Syndrome

- Described by Langdon Down in 1866
- Etiology: Trisomy 21
- Birth prevalence 1/600-1/2000
  - Most common chromosomal anomaly
- Associated with maternal age >35
- Mental retardation (IQ 30-50)
- Alzheimer’s disease (early onset, after age 35)
- Dementia (30%) 
- Short stature
- Average life expectancy 35 y
Down Syndrome

- Characteristic facial features:
  - Midface hypoplasia
  - Flat occiput
  - Flat nasal bridge
  - Up-slanting palpebral fissures
  - Epicanthal folds
  - Brushfield spots
  - Micromandibula
  - Macroglossia

Down Syndrome

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Down Syndrome

- Periodontal disease (90% of cases)
- Delayed tooth eruption of both DT, PT (75%)
- Missing teeth (23%-47%)
- Decreased parotid salivary flow rate
- Increased susceptibility to infection
- Hepatitis B antigen carrier status
- Thyroid disorders (50%, hypo or hyper)
- Hearing deficit

Down Syndrome

- Airway Concerns
  - Due to midface hypoplasia, the nasopharynx and oropharynx dimensions are smaller
    - Slight adenoid hypertrophy can cause upper airway obstruction
  - Congenital mild-moderate subglottic narrowing not uncommon
    - Post extubation stridor
  - Obstructive sleep apnea
    - Prevalence 54%-100% in Down syndrome patients
    - Combination of anatomic and functional mechanisms
      - Midface hypoplasia, macroglossia, etc
      - Hypotonia of pharyngeal muscles

Down Syndrome

- Cardiovascular anomalies (40%)
  - AV septal defect, VSD
  - Mitral valve prolapse (50% of adult)
- GI anomalies (10%-18%)
  - Tracheoesophageal fistula, pyloric stenosis, duodenal atresia
- Malignancy
  - Acute lymphoblastic leukemia (20 fold)
  - Some gonadal and extragonadal tumors

Down Syndrome

- Heart defect: 1/4 found Tetralogy of Fallot
Gingival fibromatosis
- Slowly progressive gingival enlargement caused by a collagenous overgrowth of the gingival fibrous connective tissue
- May be familial or idiopathic
- Sometimes seen with:
  - Hypertrichosis
  - Generalized aggressive periodontitis
  - Epilepsy
  - Intellectual disability
  - Sensorineural deafness
  - Hypothyroidism, chondrodystrophia, and growth hormone deficiency.

**BOX 4-5** Syndromes Associated with Gingival Fibromatosis
- Byars-Jurkiewicz syndrome
- Costello syndrome
- Cross syndrome
- Infantile systemic hyalinosis
- Jones-Hartfield syndrome
- Murray-Puretic-Drescher syndrome
- Ramon syndrome
- Rutherford syndrome
- Zimmerman-Laband syndrome

Gingival fibromatosis
- Cross syndrome: microphthalmia, cloudy corneas, hypopigmentation, athetosis
- Murray-puretic-drescher syndrome: multiple juvenile PAS-positive hyaline fibromas of the head, flexion contractures, mental retardation, elevated urinary hyaluronic acid
- Ramon syndrome: cherubism, mental retardation, epilepsy, juvenile rheumatoid arthritis
- Zimmermann Laband syndrome: ear, nose, bone - hypoplasia of the distal phalanges, joint hypermobility and nail defects with hepatosplenomegaly
- Rutherford syndrome: mental retardation, aggressive behavior, dentigerous cysts associated with congenitally enlarged gingivae and delayed tooth eruption.

Papillon–Lefèvre syndrome
- Papillon–Lefèvre syndrome (PLS), also known as palmoplantar keratoderma with periodontitis
- An autosomal recessive genetic disorder caused by a deficiency in cathepsin C (chromosome 11q14-q21)
- Cathepsin C is an enzyme which processes and activates several serine proteases critical to immune and inflammatory responses of myeloid and lymphoid cells.
- Affect junctional epithelium around the tooth.

Papillon–Lefèvre syndrome
- Advanced periodontitis in both the deciduous and the permanent dentitions
- At 4 to 5 years of age, all primary teeth typically have been lost or extracted.
- By age 15, all of the permanent teeth have been lost in most affected individuals
- *A. actinomy cetemcomitans* has been related directly to the periodontal destruction.
Haim-Munk syndrome
- Also exhibits palmoplantar keratosis, progressive periodontal disease, recurrent skin infections, and several skeletal malformations.
- More severe skin manifestations; the periodontal disease is milder.
- Also exhibit mutation of the cathepsin C gene and represent allelic variants of the mutated gene responsible for Papillon-Lefèvre syndrome.

Ramsay Hunt syndrome
- Reactivation of VZV in the geniculate ganglion
- Characterized by cutaneous lesions of the external auditory canal and involvement of the ipsilateral facial and auditory nerves.
- May exhibit facial paralysis as well as hearing deficits, vertigo, and other auditory and vestibular symptoms; develop loss of taste in the anterior two-thirds of the tongue.
- Similar associations also have been demonstrated with HSV and EBV. These findings suggest an underlying viral cause for many cases of "idiopathic" facial paralysis.

Behçet’s Syndrome
- Immunogenetic basis (HLA-B51)
- Multisystem inflammatory disease
- Oral lesions (aphthous-like ulcers)
  - Occur in 99% of the patients
  - Is first manifestation in 25%-75% of the cases
- Other lesions (in order of prevalence) genital ulcerations, cutaneous lesions, arthritis, uveitis, thrombophlebitis, GI manifestations, and CNS involvement

What other systemic disorders associated with recurrent aphthous stomatitis?
Orofacial granulomatosis

- a variety of clinical presentations that, on biopsy, reveal the presence of nonspecific granulomatous inflammation
- abnormal immune reaction
- involvement of the lips alone is called cheilitis granulomatosa (of Miescher)
- Lip lesion + facial paralysis + fissured tongue = Melkersson-Rosenthal syndrome

**Melkersson-Rosenthal syndrome:**
- Persistent enlargement of the lower lip
- Facial paralysis
- Fissured tongue

**Intraoral lesions:**
- Tongue - fissures, edema, paresthesia, erosions, or taste alteration
- Gingiva - swelling, erythema, pain, or erosions
- Buccal mucosa - cobblestone appearance of edematous mucosa or focal areas of submucosal enlargement
- Sulcus - linear hyperplastic folds often with elongated ulcerations in the base of these folds
- Palate - papules or large areas of hyperplastic tissue
- Hyposalivation rarely is reported

**Orofacial granulomatosis**

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Melanin pigmentation of oral mucosa

- Syndrome-associated pigmentation
  - Peutz-Jeghers syndrome
  - Addison’s disease
  - Myxoma syndrome
  - Bandler syndrome
  - Laugier-Hunziker syndrome or phenomenon

Peutz-Jeghers Syndrome

- Autosomal dominant trait
- Mutation (most cases) of STK11 (also known as LKB1 gene on 19p13.3 (serine-threonine kinase)
- New mutations 35%
- Skin freckle-like lesions:
  - Usually develop early in childhood
  - Periorificial areas (mouth, nose, and genital region)
- Oral lesions:
  - Vermilion zone, labial & buccal mucosa, tongue
  - 1-4 mm brown to blue-gray macules

Addison disease

- Primary adrenocortical insufficiency
- May result from adrenal gland infection (tuberculosis), autoimmune disease, or idiopathic causes
- With reduced cortisol production by the adrenals, pituitary adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH) increase as part of a negative feedback mechanism.
- Larger melanotic macules with weakness, weight loss, nausea, vomiting, and hypotension.

Myxoma Syndrome

- Autosomal-dominant
- Includes soft tissue myxomas (as well as oral, cutaneous, and cardiac myxomas) and endocrinopathies.

Bandler Syndrome

- Melanotic macules of the oral mucosa & perioral region + hemangiomas of the small intestine + mucocutaneous pigmentation.
Laugier-Hunziker syndrome
- or phenomenon
- is a rare acquired pigmented disorder that presents as lip, oral, or finger macules and subungual (nail bed) melanocytic streaks. Pigmentation of the conjunctiva and penis has been described in patients with this syndrome.

Neurofibromatosis type I
- Common hereditary condition ~1 in 3,000 births
- Known as von Recklinghausen disease of the skin
- Autosomal dominant trait
- Accounts for 85%-97% of neurofibromatosis cases
- Mutation of NF1 gene on 17q11.2 (neurofibromin – tumor suppressor protein)
- Some associated with Noonan syndrome or with central giant cell granulomas of the jaw

### Neurofibromatosis type I
- Café au lait pigmentation
- Neurofibromas (plexiform variant – pathognomonic)
- Axillary or inguinal freckles
- Lisch nodules (translucent brown-pigmented spots on the iris - hamartoma)
- Hypertension
- Other possible abnormalities: CNS tumors (optic glioma), macrocephaly, mental deficiency, seizures, short stature, scoliosis

### Oral manifestation:
- 72%-92% of cases
- Enlargement of the fungiform papillae (most common, 50%) – specificity for NF1 is unknown
- Intraoral neurofibromas (25%-37%)

### Complications: cancer development
- Malignant peripheral nerve sheath tumor
  - Occur in ~5% of cases
  - Most common on the trunk and extremities
  - Poor prognosis; 5 years survival ~35%-54%
- Other malignancies: CNS tumors, pheochromocytoma, leukemia, rhabdomyosarcoma, Wilms' tumor
- Average lifespan of patient with NF1 = 8-15 years less than the general population, mostly related to vascular disease & malignant neoplasms
Neurofibromatosis type II

- also known as MISME syndrome – multiple inherited schwannomas, meningiomas, and ependymomas
- autosomal dominant mode of transmission
- mutations of Merlin or Schwannomin gene located on chromosome 22 band q11-13.1
- The main manifestation of the condition: bilateral schwannomas of the auditory-vestibular nerve (cranial nerve viii that transmits sensory information from the inner ear to the brain).

Diagnosis of NF2:
- Prenatal: bilateral vestibular schwannomas
- Postnatal:
  - bilateral vestibular schwannoma (VS) or family history of NF2 plus unilateral VS or any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities
  - unilateral VS plus any two of meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities
  - Two or more meningioma plus unilateral VS or any two of glioma, schwannoma and cataract.

Another set of diagnostic criteria is the following:
- Detection of bilateral acoustic neuroma by imaging procedures
- First degree relative with NF2 and the occurrence of neurofibroma, meningiomas, glioma, or Schwannoma
- First degree relative with NF2 and the occurrence of juvenile posterior subcapsular cataract.
- The criteria have varied over time. The last revision of the NF2 criteria was done by M.J. Smith in 2017. This included the consideration of a LZTR1 mutation (schwannomatosis) instead of NF2 and excluded bilateral vestibular schwannomas that occur after 70 years of age.

Classification into 2 forms:
- The Wishart-Phenotype - multiple cerebral and spinal lesions in people <20 years with rapid progression of the tumors.
- single central tumors with slow progression after age of 20 are thought to have the Feiling-Gardner-Phenotype.
- The principal treatments: neurosurgical removal of the tumors and surgical treatment of the eye lesions.

Multiple endocrine neoplasia syndrome

- Autosomal dominant trait, 50% spontaneous mutations
- Mutation in the RET proto-oncogene, chromosome 10
- Marfanoid body build (narrow face, elongated limbs with muscle wasting)
- Mucosal neuromas
  - Small, pedunculated neuromas on conjunctiva, eyelid margin, cornea
  - Oral mucosal neuromas – the first sign of MEN2b
  - Bilateral neuromas of the commissural mucosa – highly characteristic
Multiple endocrine neoplasia type 2B
- Adrenal pheochromocytomas (50%): bilateral or multifocal
  - result in profuse sweating, intractable diarrhea, headaches, flushing, heart palpitations, and severe hypertension
- Medullary thyroid carcinoma (>95% or 100%)
  - very aggressive cancer
  - from parafollicular cells (C cells) – calcitonin production
  - most often diagnosed between 18-25 y
  - marked propensity for metastasis
  - average age at death from this cancer is 21 y
- Lab investigation:
  - Increased levels of urinary vanillylmandelic acid (VMA)
  - Increased epinephrine-to-norepinephrine ratios
  - Elevated serum or urinary levels of calcitonin
  - tell onset of the tumor
  - for monitoring to detect local recurrences or metastases after treatment

Ehlers-Danlos Syndrome
- Abnormal collagen production
- Easily Bruising
- Joint hypermobility
- Hyperelasticity or hyperextensibility of the skin
- Papyraceous scarring of skin
- 80% = classic type (mutation colIV)
Ehlers-Danlos Syndrome

Oral manifestations:
- Gorlin sign – 50%
- Oral mucosal friability - easily bruising and bleeding
- Tendency for recurrent subluxation of the TMJ
- Hypodontia / Hyperdontia
- Large pulp stones
- Premature gingival recession (tooth attachment loss) – type IV, VIII

Tuberous sclerosis

- Characteristics: mental retardation, seizure disorders, angiofibromas of skin
- AD; mutations TSC1 (on chromosome 9) or more commonly TSC2 (on chromosome 16)
- TSC1 & TSC2 have tumor suppressor function

Tuberous sclerosis

- Skin lesions:
  - Earliest skin sign - congenital white, hypopigmented ash-leaf-shaped macules on the trunk and limbs
  - During first decade - pink-red papules or nodules, most prominent in the nasolabial folds, cheeks, forehead, and scalp = angiofibromas
  - Angual or peringual fibromas (around or under the margins of the nails)
  - Orange-peel-like shargreen patches in the lumbar area

Tuberous sclerosis

- Oral lesions:
  - Enamel pitting on facial surface of anterior teeth (50%-100%)
  - Multiple fibrous papules (11% - 56%) at anterior gingiva (predominant), lip, buccal mucosa, palate, tongue
  - Diffuse fibrous gingival enlargement
  - Intrabony fibrous or myxomatous tumors of the jaws also may occur
Tuberous sclerosis

- Management of tuberous sclerosis often is directed primarily at controlling the associated seizures.
- Periodic MRI of the head to screen for intracranial lesions.
- In general, patients have a slightly reduced life span with death sometimes related to complications of central nervous system and kidney disease.

Multiple Hamartoma Syndrome

- Cowden syndrome
- Autosomal dominant, rare condition
- Mutation of PTEN gene on chromosome 10

Multiple Hamartoma Syndrome

- Skin lesions: second decade
  - multiple, small (<1 mm) papules on facial skin around the mouth, nose, and ears (trichilemmomas)
  - warty appearing growth on dorsal surface of hand (acral keratosis)
  - prominent callus-like lesion on the palms or soles (palmoplantar keratosis)
  - cutaneous hemangiomas, neuromas, xanthomas, lipomas

Multiple Hamartoma Syndrome

- Oral manifestations:
  - multiple papules affecting gingivae, dorsal tongue, buccal mucosa (fibroepithelial hyperplasia)
  - high palatal arch, periodontitis, extensive dental caries

Multiple Hamartoma Syndrome

- Other problems:
  - Thyroid: goiter, thyroid adenoma, adenocarcinoma
  - Breast: fibrocystic disease, breast cancer (25%-50%; mean age 40 y)
  - GI – multiple benign hamartomatous polyps
  - Benign & malignant tumors of female genital urinary tract

Multiple Hamartoma Syndrome

- Diagnosis on finding of 2 of 3 prognomonic signs:
  - Multiple facial trichilemmomas
  - Multiple oral papules
  - Acral keratoses
**Plummer-Vinson Syndrome**
- Iron-deficiency anemia + glossitis + dysphagia
- High frequency of oral & esophageal SCC
- Anemic symptoms: fatigue, shortness of breath, and weakness
- Lab findings
  - Hypochromic microcytic anemia
- Burning sensation with diffuse papillary atrophy of the dorsum tongue
- Angular cheilitis

**Burning Mouth Syndrome**
- Burning mouth syndrome is the medical term for ongoing (chronic) or recurrent burning in the mouth without an obvious cause.
- New (Neville 2016): BMD
- Burning mouth disorder is a confounding pain condition, neuropathic in nature with both peripheral and central components.

**Sjögren’s syndrome (SS)**
- Female: male ratio = 9:1
- Autoimmune disorder
  - HLAs: HLA-DRw52, HLA-B8, HLA-DR3
  - Viruses: EBV, HTLV-1
- Dry mouth symptoms: difficulty swallowing, altered taste, or difficult in wearing dentures
- Oral mucosal changes: fissured & atrophic tongue papillae, red & tender (secondary candidiasis), related denture sore mouth and angular cheilitis
- Cervical caries

**Sjögren’s syndrome (SS)**
- Diffuse, firm enlargement of the major salivary glands (30%-50%)
  - bilateral, nonpainful or slightly tender, intermittent or persistent in nature with increased risk for retrograde bacterial sialadenitis
- Sialographic exam reveals punctate sialectasia & lack of normal branching of the ductal system = “fruit-laden, branchless tree”
Sjögren's syndrome (SS)

- Scintigraphy with radioactive technetium-99m pertechnetate characteristically shows decreased uptake and delayed emptying of the isotope.

- Other possible problems: dry skin and other mucosae, fatigue, depression, lymphadenopathy, primary biliary cirrhosis, Raynaud's phenomenon, interstitial nephritis, interstitial lung fibrosis, vasculitis, and peripheral neuropathies.

- Laboratory values:
  - Elevated serum ESR, IgG levels
  - Presence of RF (60% of cases), ANAs (75%-85%)
  - Nuclear autoantibodies: anti-SS-A (anti-Ro; 50%-76%) and anti-SS-B (anti-La; 30%-60%) - in primary SS
  - Salivary duct autoantibodies – in secondary SS.

- Histopathology:
  - Basic microscopic finding = Lymphocytic infiltrate of the salivary glands leads to destruction of the acinar units.
  - Biopsy of normal minor salivary glands of lower lip - focal lymphocytic infiltration (a focus of >50 lymphocytes) adjacent to normal appearing mucous acini within a 4 mm² area of glandular tissue.
  - Found consistently in most of the glands in the specimen.

- Other possible problems: dry skin and other mucosae, fatigue, depression, lymphadenopathy, primary biliary cirrhosis, Raynaud’s phenomenon, interstitial nephritis, interstitial lung fibrosis, vasculitis, and peripheral neuropathies.

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  - Salivary duct autoantibodies – in secondary SS.

- Benign lymphoepithelial lesion: in more advanced lesions.
  - Acini are destroyed but the ductal epithelium persists.
  - Ductal cells & surrounding myoepithelial cells become hyperplastic, forming epimyoepithelial islands, throughout the lymphoid proliferin.
Sjögren’s syndrome (SS)

Treatment and prognosis:
- Supportive treatment
- Lifetime risk for lymphoma of 5% to 15% = 20 times greater than the general population
  - Extranodal marginal zone B-cell lymphomas of MALT type
  - High-grade lymphoma

Frey Syndrome

- Auriculotemporal syndrome
- Aberrant neuronal regeneration
- Facial flushing + sweating along the distribution of auriculotemporal nerve
- Minor’s starch-iodine test

Syndrome and cancer

- Down syndrome
- Peutz-jeghers syndrome
- NF1
- MEN 2B
- Multiple hamartoma syndrome
- Plummer-Vinson syndrome
- Sjögren syndrome

END