RhAPP

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Pediatric Sjogren's

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Faculty Disclosures

- Debbie Durkee, MSN, FNP-c:
  - There are no relevant financial relationships to disclose.

Objectives

1. Understand that currently there is no gold standard diagnostic test, criteria, or classification for pediatric SS.
2. Identify that SS should be strongly considered in the DDx of a child with recurrent parotid swelling.
3. Understand that SS should be considered in a pt who is RF+ and/or has SLE-like labs w/o evidence of SLE.
4. Understand that symptoms and presentations of pediatric sjogren's are variable.
5. Identify 3 routine monitoring recommendations for a pt with sjogren's.

What is Sjogren's Syndrome (SS)

- A heterogeneous chronic multisystem autoimmune rheumatic condition
- Manifestations range from localized glandular disease to complex systemic and organ involvement
- Chronic autoimmune disease characterized by inflammation of the exocrine glands
- Principal targets: salivary and lacrimal glands → resulting in dryness of the mucosal surfaces
- Potential for extensive exocrinopathy affecting the skin, respiratory tract, and urogenital tract
- Primary pathological finding is lymphocytic infiltration of affected tissues
- Salivary gland biopsies: focal aggregates of lymphocytes, plasma cells, and macrophages

Primary vs Secondary

- Primary
  - no association with other autoimmune disease
  - pSS
- Secondary
  - presence with another autoimmune disease
  - most commonly SLE and RA
  - sSS
- Sjogren’s disease or Overlap
  - Sjogren’s foundation

Epidemiology

- To date, there have been no large population studies reporting accurate incidence or prevalence of primary Sjogren's in childhood

- Similar to adults:
  - female predominance- 5:1 to 7:1
- Mean age initial symptoms were reported:
  - 10 years
- Mean age of diagnosis:
  - 12 years

Virdee S, Greenan-Barrett J, Ciurtin C. A systematic review of primary Sjogren's syndrome in male and pediatric populations. Clin Rheumatol . 2017;36:2225–2236.

Hammenfors D.S, Valim V, Bica B.E.R.G, et al. Juvenile Sjogren's syndrome: clinical characteristics with focus on salivary gland ultrasonography. Arthritis Care Res . 2020;72(1):78–87.

Diagnosing Pediatric Sjogren's

Diagnosing pediatric sjogren's is challenging:

- currently no gold standard diagnostic test
- many of the cardinal symptoms are common

Since 2002, three classification criteria sets have been developed:

- American-European Consensus Group (AECG) criteria in 2002
- American College of Rheumatology-Sjögren International Collaborative Clinical Alliance criteria (ACR-SICCA) in 2012
- **ACR-European League Against Rheumatism (EULAR) classification criteria in 2016**

Of note:

- these classification criteria are not intended to be applied as diagnostic criteria
- they have never been tested in children with pSS
- recommendations are for using modified ACR-EULAR 2016

ACR-EULAR Classification Criteria for Primary Sjögren

The classification of primary Sjögren syndrome (pSS) applies to any individual who meets the inclusion criteria, does not have any of the exclusion criteria, and has a score ≥4 from the following items:

Item	Weight/score
Labial salivary gland with focal lymphocytic sialadenitis and focus score >1	3
Anti-SSA (Ro)+	3
Ocular staining score ≥5 on at least one eye	1
Schirmer ≤5 mm/hr on at least one eye	1
Unstimulated whole saliva flow rate ≤0.1 mL/min	1

Shiboski S.C, Shiboski C.H, Criswell L.A, et al. American College of Rheumatology classification criteria for Sjogren's syndrome: a data-driven, expert consensus approach in the SICCA cohort. Arthritis Care Res . 2012;64:475–487.

Proposed Criteria for Juvenile Primary Sjögren Syndrome

Bartunkova et al. 9 proposed a set of criteria for the diagnosis of pSS in children, but these have not been validated or widely accepted

Presence of four or more criteria required for diagnosis

- I. Clinical symptoms
  - 1. Oral- dry mouth, recurrent parotitis, or enlargement of parotid glands
  - 2. Ocular-recurrent conjunctivitis without obvious allergic or infectious etiology, keratoconjunctivitis sicca
  - 3. Other mucosal involvement-recurrent vaginitis
  - 4. Systemic-fever of unknown origin, non-inflammatory arthralgias, hypokalemic paralysis, abdominal pain
- II. Immunological abnormalities
  - 1.Presence of at least one of the following: anti-SSA, anti-SSB, high-titer ANA, RF
  - III. Other laboratory abnormalities or additional investigations
- III. Other laboratory abnormalities or additional investigations
  - 1. Biochemical- elevated serum amylase
  - 2. Hematological- leukopenia, high ESR
  - 3. Immunological- polyclonal hyperimmunoglobulinemia
  - 4. Nephrological- renal tubular acidosis
  - 5. Histological proof of lymphocytic infiltration of salivary glands or other organs
  - 6. Objective documentation of ocular dryness-Bengal red staining, Schirmer test
  - 7. Objective documentation of parotid gland involvement- sialography
- IV. Exclusion of all other autoimmune diseases

Bartunkova J, Sediva A, Vencovsky J, et al. Primary Sjogren's syndrome in children and adolescents: proposal for diagnostic criteria. Clin Exp Rheumatol . 1999;17(3):381–386.

Obstacles in Making the Diagnosis

- Diagnosing pediatric sjogren's can be challenging:
  - Ocular and oral dryness
  - May be impossible to meet criteria
  - Children produce more saliva and tears naturally
  - Dryness can take years to develop
- Diagnostic goals:
  - Autoimmunity and dryness factors
  - Finding biomarkers: ideally for diagnosis, prevent the development of dryness
  - Dryness monitoring

Clinical Manifestations of Sjögren Syndrome

Dry eyes	Keratoconjunctivitis sicca Corneal ulcers, keratitis
Dry mouth	Increased caries
Major salivary gland swelling	Parotid Submandibular
Extraglandular manifestation	Fatigue Arthritis Arthralgia/myalgia Raynaud phenomenon
Pulmonary involvement	Chronic cough Interstitial lung disease: nonspecific interstitial pneumonia, Lymphocytic interstitial pneumonia, usual interstitial pneumonia Small airway disease
Renal involvement	Tubulointerstitial nephritis
Neurological involvement	Peripheral neuropathy Central nervous system disease: demyelinating disease, neuromyelitis optica

Table 29.1 Petty, Ross, E. et al. Textbook of Pediatric Rheumatology E-Book. Available from: Elsevier eBooks+, (8th Edition). Elsevier - QHCE, 2020

Oral Manifestations

- Xerostoma:
  - dryness of the oral mucosa, 90% of adults with SS
- Poor oral salivary flow ➡ difficulty swallowing dry food, changes in taste, halitosis, increased dental caries
- Parotid enlargement:
  - 2/3 of adults
  - most common presenting feature in children 50-70%
  - **recurrent parotitis may be the only complaint**
  - unilateral but often becomes bilateral
  - painful or painless
  - most often episodic, but it may be chronic in some patients.
- pSS should be strongly considered in the DDx of a child with recurrent parotid swelling

Ocular Manifestations

- Decreased tear production ➧ damage to the corneal and bulbar epithelium (keratoconjunctivitis sicca)
- Children may have difficulty describing ocular symptoms
- Described as:
  - burning sensation
  - foreign body sensation
  - ‘sandy’ or scratchy feeling under eyelids
  - itchiness
- Can be associated with erythema and/or photosensitivity
- Exam findings:
  - corneal erosions or scarring
  - insufficient tear volume

Extraglandular manifestations

- May be less common in children
- Fatigue, low grade fever, myalgia, arthralgia
- May be more common at the time of parotitis
- 2 pathophysiologic groups:
  - Peripheral organ involvement due to lymphocytic invasion in the epithelia of organs other than exocrine glands (interstitial nephritis and obstructive bronchiolitis)
  - Extraepithelial involvement secondary to immune complex deposition and subsequent inflammation

Skin, Nose, Ears, and Joints

- Skin Manifestations:
  - dryness
  - Raynaud's
- Raynaud's phenomenon
  - relatively common among individuals with SS
  - may precede sicca complaints by years
  - limited literature in pediatric patients with SS, may not be as common in children
- Nose
  - epistaxis
- Ears
  - dryness, pruritis
- Joint manifestations:
  - arthritis, arthralgia
- Difficult to determine frequency in children
  - In Virdee et al. joint involvement was reported in 10% to 57% of children, however, it is not clear if this was arthralgia or arthritis
- Adults
  - commonly report arthralgia, and inflammatory arthritis is reported in ~20%

Pulmonary involvement

- 9% to 20%: clinically significant lung involvement
- 43% to 75%: lung disease if investigated further
- May be present with cough and dyspnea
- Can be asymptomatic early on
- Dryness in upper respiratory tract or oropharynx ➡ hoarseness, bronchitis, or pneumonitis
- Dryness of the epithelium of trachea ➡ chromic dry cough
- Lymphocytic infiltration around bronchi and bronchioles ➡ small airway obstructive disease and airway hyperactivity

- ILD: ~8% of adults, appearance of lymphocytic interstitial pneumonitis
- CXR less sensitive than HRCT: inter- and intalobular thickening and ground glass appearance in lower lung fields

- PFTs: can demonstrate lung impairment (restrictive pattern) or airway impairment (obstructive pattern), decreased peak flows or diffusing capacity

- Pulmonary arterial hypertension, less common
- Hilar and/or mediastinal adenopathy or lung nodules
- Nodules: Bx to r/o lymphoma

Renal involvement

- Renal manifestations are less common
- Interstitial Nephritis
  - resulting from activated lymphocytes infiltrating tubular epithelium
  - can result in distal RTA with hyposthenuria
  - a review of 12 children with pSS, renal tubular acidosis was more frequently seen in children than in adults
- Glomerulonephritis
- More rare manifestations:
  - proximal tubular acidosis
  - membranous or membranoproliferative glomerulonephritis
  - tubulointerstitial nephritis
  - interstitial cystitis

Neurologic involvement

Broad spectrum of manifestations including:	Peripheral nervous system manifestations	Central nervous system (CNS) manifestations can be either:	Demyelinating CNS disease:
•either the peripheral or central nervous system	•A broad range of mono- and poly-neuropathies •A syndrome of purely sensory neuropathy is relatively unique to SS and has been reported in childhood •A peripheral neuropathy may precede the appearance of sicca symptoms in some patients •There have been reports of optic neuropathy in pediatric-onset SS	•Diffuse: encephalopathy, inflammatory meningitis, or cognitive or psychiatric changes •Focal/multifocal: seizures, hemiparesis, movement disorders, brainstem, motor neuron, and cerebellar syndromes	•Neuromyelitis optica spectrum disorder (NMOSD) has been reported in association with pSS •Several reports of children affected •Characterized by recurrent episodes of optic neuritis or extensive transverse myelitis, frequently associated with the presence of antiaquaporin-4 IgG antibodies

MS like symptoms = consider sjogren’s

Reproductive

- Vaginal dryness

- +Anti Ro (SSA) and/or Anti La (SSB) Abs:
  - Counseling older adolescents with SS and anti-Ro/La antibodies about the risk of neonatal lupus in future pregnancies
  - More intensive pregnancy screening for teenagers with SS who become pregnant
  - Neonatal lupus: maternal dx of SS is as common as lupus
  - Congenital heart block

Labs

- Very elevated ESR, may be related to significant hypergammaglobulinemia
- Majority have a +ANA
- RFs are found in 22% to 66% of pediatric patients
- Approximately 20% of adults with SS have cryoglobulins in their serum
  - an indicator of poor prognosis, a higher risk of developing additional organ involvement and with a greater potential for developing lymphoma
- SSA/SSB:
  - “hallmark” feature of this disease
  - found in only 50% to 70% of patients
  - associated with a higher prevalence of systemic, hematological, and immunological abnormalities, as well as the possibility of neonatal lupus in offspring

Imaging

Sialometry

- Measures salivary flow
- Procedure is difficult to do, particularly in younger children
- No appropriate age-matched normal values for children

Sialography:

- A radiocontrast method of examining the anatomical detail of the parotid ductal system
- Requires cannulation of the main salivary ducts and injection of radio-opaque dye
- Radiographic features of SS range from punctuate or globular ectasia sialectasis to considerable narrowing of the ductal system and destroyed parenchyma
- Sialography is not included in either AECG or 2016 ACR/EULAR classification criteria
- Used less frequently

Salivary gland scintigraphy:

- Assesses salivary gland function
- Uptake and secretion of the isotope is delayed or absent in patients with SS
- It is not part of the 2016 ACR/EULAR classification criteria
- Becoming less popular

Imaging

Salivary gland ultrasound (SGUS):

- Increasingly utilization and noninvasive
- Identifies abnormal salivary gland architecture
- Similar accuracy to sialography or scintigraphy
- **Primary tool for pediatric evaluation and monitoring**

Simple scoring system

- Developed by de Vita et al.
- Commonly used
- Based on parotid gland homogeneity and presence of hypoechoic lesions
- Grading on a scale 0 (normal gland) to 4 (multiple hypoechogenic areas greater than 6 mm or multiple calcifications with echogenic bands)
- A score of grade 3 or 4 is considered most suggestive of a diagnosis of pSS

Biopsy

Minor salivary glands of the lower lip:

- Has been used widely as a diagnostic tool, particularly for adults with a presumptive diagnosis of SS
- Findings of periductal lymphocytic infiltration or chronic sialadenitis indicate a diagnosis of SS
- Specific criteria being focal lymphocytic sialadenitis, with a focus score of 1 or greater per 4 mm
- May be non diagnostic or may not provide adequate glandular tissue for evaluation

Parotid gland:

- More definitive
- Potentially lower risk compared to labial biopsy
- Parotid swelling can be identified when the minor salivary biopsy is normal
- Can be a safe method of confirming the diagnosis of SS in the pediatric population

Biopsy findings

Focus scores:

- 50 lymphocytes or more in a 4 mm2 area
- Focused = clumped together
- Classified on a scale from grade 0 to grade 4
- A score of 1 is diagnostic for SS
- Higher scores are associated with a higher risk for MALT lymphoma

Pediatrics:

- Study looking at pediatric biopsies
- **Focal lymphocyte infiltrates**
- Score <1 or 50 per mm2 = 0.8 or 35 per mm2

**** IgG4 staining with Bx

Ocular evaluation

Schirmer test:

- A standardized, valid method of testing the amount of tear secretion
- A small specially measured strip of filter paper is slipped under the inferior lid of the eye for 5 minutes
- Then the wet length of the paper is measured
- A tear secretion of less than 5 mm indicates a significant decrease in tear secretion
- May be difficult to complete in many children

Rose Bengal or Lissamine green staining

- Dyes the corneal and conjunctival epithelium damaged secondarily to low tear output
- Performed by an ophthalmologist
- Not validate in young children
- Used less frequently

Ocular Staining Score (OSS):

- Corneal and conjunctiva staining
- **Conjunctival staining** = 1st place for erosive changes
- If only cornea staining = false negative test result
- Score of 5 or greater indicates dryness
- Pediatrics = more challenging to meet this criteria

Treatments

- The SS disease course is often more indolent in comparison to other rheumatologic conditions, such as SLE
- May not require immunosuppressive therapy if there is no extraglandular disease.
- Treatment may be focused on symptom relief:
  - dry eyes, dry mouth, recurrent parotitis
- Eyes:
  - Artificial tears, topical cyclosporine, cholinergic (Pilocarpine) to increase tear and saliva production
  - **Annual ocular screening if asymptomatic to monitor for damage**
  - Avoidance of conditions that increase dryness (smoking, anticholinergic medications)
- Mouth:
  - Sugar-free lozenges or chewing gum to help increase salivation
  - **Good dental hygiene and routine dental exams**
  - Dry mouth may be challenging, tends to be rare in pediatrics
- Plaquenil:
  - May be helpful in treating constitutional symptoms, arthralgias, and fatigue
  - One study showed a significant increase in saliva production after 6 months of treatment.
  - There have been conflicting results from other reported studies, some suggestions of improvement in ocular or oral symptoms
  - Few studies demonstrating improvements in laboratory parameters
  - **Seems to be most helpful for joint pain**

Treatments

- Immunosuppressives:
  - Are not uniformly required
  - Extraglandular organ manifestations, severe ocular/mucosal sx, or disabling constitutional sx may require more aggressive tx
- Corticosteroids:
  - Recurrent parotitis, systemic sx (fatigue/arthralgia)
  - Does not stop the progression of SS or improve salivary flow
- MTX:
  - 1 trial in adults indicated some improvement in clinical symptoms and decreased parotid gland swelling
  - Not frequently used
- Biologics:
  - increasing evidence demonstrating effectiveness
- TNFi
  - Variable responses
  - Etanercept-/Infliximab+
- **Abatacept**:
  - In 15 subjects treated for 24 weeks, there was significant reduction of disease activity and improvement in patient-reported symptom

Long term outcomes

- A heterogeneous chronic multisystem autoimmune rheumatic condition
- Mild to Severe
- Most significant and longest impact: dryness
  - Mouth and eyes
  - Saliva and tear production: normal, protective
  - “can’t stop thinking about” the dryness:
- More complex: ILD, MS, Lupus-like, MALT lymphoma
- Has not been studied in pediatrics

Lymphoma

- Lymphoma:
  - MALT lymphoma: slow growing d/t chronic inflammation (stomach, lung, thyroid, **salivary glands**)
  - Hallmark organ: salivary glands
  - 20x the risk
  - Unknown prevalence in children, does occur
  - Often presenting with pain, fatigue, dryness

MH 11 yr old male: Dacryoadenitis

June 2019: right eye erythema, pain, swelling, photosensitivity

- 2 local optometrists: cellulitis, Abx and topical steroids
- 3rd optometrist: pink eye, stopped steroid drops
- PCH: CT, periorbital cellulitis, IV Abx, sx improved then resolved, DC'd 4 days later
- Ocular sx recurred several days later
- Moran: MRI and Bx, prednisone, referred nonspecific orbital inflammation, elevated IOP
- Recurrence of sx each time prednisone was stopped and eventually with weaning
- NPV Sept: Prednisone 10 mg
- No: systemic, GI, joint sx
- PE: unremarkable
- Tx: Humira, Prednisone (7/2020), considered Rituxan (11/2019), Plaquenil, Orencia

- CT Orbits: 1. Right pre and post septal orbital cellulitis. No subperiosteal abscess.
- 2. Mild enlargement of the adenoids. Otherwise, normal CT of the orbits
- MRI: nl
- Bx: biopsy was obtained and indicated mild dacryoadenitis of the right lacrimal gland.
- CBC, CMP, CRP, dDimer, CK, Aldolase ACE, Lysozyme, nl
- ESR 18-->2
- ANA, RF, ANCA, negative
- IgG, IgA, IgM, IgG subclasses nl
- IgG4 staining negative
- B2 microglobulin nl

- DDx: IgG4 related systemic disease, Sjogren's, neuro sarcoidosis, GPA, orbital pseudotumor
- Lacrimal gland bx reviewed for lymphoproliferative process: focus score 1.33

MM 16yr old: coincidentally discovered parotitis

June 2018: jaw pain x 1 year

- Right TMJ pain and difficulty opening mouth started summer 2017
- Intermittent over the year prior to clinic visit
- Subsequently developed similar sx in left TMJ
- Sx progressed and began occurring daily by 2/2018
- Seen by TMJ specialist, bony changes, referred
- Intermittent ankle pain
- Purple and red color changes in hands/feet associated with numbness, tingling, pain
- PE: oral excursion 3 cm with POM, tenderness, condyle flattening, and slight deviation to the right
- No hx dry eye/mouth, dental caries
- Tx: Enbrel, nifedipine, Plaquenil
- 10/2019: parotid swelling, pain, dry mouth, dry eye
- Prednisone 3-5 days for flares
- Tx: MTX vs Orencia

- CT: 50% bone loss on right and 40% on left
- MRI: B/L changes of chronic TMJ synovitis, left > right, mild diffuse active synovitis
- MRI review: B/L enlarged, edematous parotid gland with a little enhancement as well as displaced TMJ meniscus, condyle irregularity, mild-moderate synovitis B/L
- CBC unremarkable, CMP nl
- ESR 30
- CRP 0.9
- ANA <1:80
- RF, antiCCP, SSA/SSB negative
- IgG and IgG subclasses normal
- Ophtho: nl
- Bx: focus score of 1 and histologically consistent with sjogren's syndrome

AB 16 yr old: RF+ Poly JIA/SS with significant dental involvement

January 2019: pain, stiffness, swelling in fingers

- 3 mo of finger swelling, then developed pain/stiffness as well as additional joint involvement
- No dy eye/mouth, numerous dental caries started around the same time as joint sx
- PE: polyarticular arthritis, oral excursion 2.5 cm, poor dental hygiene
- 4/2019: urinary frequency w/o hematuria or dysuria
- 7/2019: dry eye, mouth sores (after starting MTX)
- Tx: prednisone (3/2019), MTX, Humira, Plaquenil, Orencia
- 10/2020: sjogren's clinic- dental/eye exams, continued orencia and plaquenil, nystatin swish/spit, salivary bx and sialoendoscopy
- Tx changed to Rituxan: persistent arthritis and increasingly symptomatic gland inflammation
- Notable dental decay→breaking/root canals→dentures
- Developed vaginal dryness and irritation, kenalog ointment
- Clotrimazole lozenges helpful with mouth sores/pain
- Pilocarpine and cyclosporine for eye dryness
- Poor wt gain, tinnitus, N/T in extremities, HAs
- CBC unremarkable
- ESR 70
- ANA 1:160; SSA 60 102
- Cr: 0.98 (4/2019), 1.06 (7/2019)
- XR: mild joint space narrowing PIPs
- US: subtle heterogeneous echogenic texture of B/L submandibular glands, which could represent mild or early inflammation; parotid glands w/ nl homogeneous echotexture and a few scattered intraparotid LNs B/L
- MRI: acute and chronic inflammation B/L TMJs, active edema and enhancement. Significant flattening and erosions
- Review of MRI: severe flattening/broadening of condyle, BM enhancement, erosions, moderate synovitis, submandibular and left parotid changes suggest salivary gland inflammation
- Sialoendoscopy: sludge in right parotid duct
- Bx: chronic sialoadenitis

BS 5 yr old: Recurrent Parotitis

July 2023: recurrent parotitis with +bx

- 1 year hx of 'flare ups' of sneezing, red watery swollen eyes, cheek and neck swelling (L>R)
- Associated with fatigue, difficulty concentrating, and decreased appetite
- Occurred weekly, could last up to 5 days
- Antibiotics had been given previously and helped with sx but flares continued
- ENT on 6/12: salivary gland bx with sialadendosopy and steroid injection of parotid gland
- No flares following steroid injection
- Reports leg and heel pain, requests to be carried
- Intermittent dry mouth, hx of numerous cavities (4-5 each visit)
- Intermittent dry, itchy eyes
- Fever with 1 flare up, also axilla and posterior knee pain
- Intermittent HAs

- PE: cervical and supraclavicular LAD, asleep by end of clinic visit
- Lymphopenia: WBC 7.5, ALC 2.5
- CMP, ESR, CRP, UA nl
- ANA 1:320 all reflex Abs negative
- RF negative
- C3 nl C4 12
- Bx: focus score greater than 1
- US: heterogeneous appearance of parotid and submandibular salivary glands w/ multiple hypoechoic areas throughout the parenchyma, no diffuse enlargement or hyperemia

- Started on Plaquenil
- Prednisone x5 days for flare
- >4 acute episodes/yr or >1/month → consider advancing treatment by adding DMARD/Biologic
- Routine dental hygiene and dental exams
- Routine ophthalmology exams
- Yearly SGUS

Looking to the Future

- Treatments:
  - In the works
  - 5-10 years for adults
  - Trickle down for pediatrics
  - No current studies for pediatric treatments
- Sjogren's Foundation:
  - Website
  - Here at RhAPP
  - Exciting frontier
  - More research
  - Prospective study
    - Registry, outcomes
    - Recruit/involvement: deborah.durkee@hsc.utah.edu

Resources

- Bartunkova J, Sediva A, Vencovsky J, et al. Primary Sjogren's syndrome in children and adolescents: proposal for diagnostic criteria. Clin Exp Rheumatol . 1999;17(3):381–386.
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Thank you