Morphoea

Paediatric morphoea is different from adult morphoea:

- More severe disease
- Linear morphoea most common
- More likely to have extra-cutaneous manifestations
- Longer disease duration
- 1/3 with active disease >10 years
- Periods of remission and disease reactivation

What extra-cutaneous manifestations do you have to worry about in children?

Neurological Manifestations

- Neurologic manifestations occur in 20-40%.
- Most common with EDS and PRS.
- Signs and symptoms:
  - Seizures
  - Headaches
  - Neuropathy
  - Behavioural changes
  - CNS vascular malformations
  - Asymptomatic MRI abnormalities
- There is poor correlation between symptoms and MRI findings.

Children’s Hospital of Wisconsin experience (32 children, 21 with neuroimaging):

- Only 2 abnormal brain MRI in 9 children with neurologic symptoms.
- Only 2 children had neurologic symptoms out of 4 children with brain MRI abnormalities.

Mayo Clinic experience (88 adults and children):

- 72 patients were evaluated by neurology.
- 40% had neurologic abnormalities.
- 44% had neuroimaging.
- 43 had neuroimaging.
- 44% had abnormal imaging.
- Poor correlation between MRI findings and neurologic symptoms.
- 48% of those with neurologic symptoms had normal MRI.
- 23% with abnormal MRI had no neurologic symptoms.
- Most MRI findings were bilateral.
- No progression with time despite cutaneous progression.
What extra-cutaneous manifestations do you have to worry about in children?

Musculoskeletal manifestations
- Musculoskeletal manifestations occur in 20-50%.
- Most common with linear morphea on limbs.
- Signs and symptoms:
  - Arthralgias
  - Arthritis
  - Joint contracture
  - Joint length and girth discrepancy
  - Functional limitations

Ocular manifestations
- Ocular manifestations occur in 2-3%.
- Most common with ECDS and PRS.
- Signs and symptoms:
  - Anterior uveitis, episcleritis, keratitis
  - Acquired glaucoma
  - Xerophthalmia
  - Strabismus
  - Mydriasis
  - Papilloedema

Linear morphea and early disease onset are risk factors for extra-cutaneous manifestations

<table>
<thead>
<tr>
<th>Linear Morphea</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Morphea</td>
<td>22.3 (2.8 - 178)</td>
<td>0.0035</td>
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<tr>
<td>Onset &lt; 10 years</td>
<td>10.0 (2.1 - 47.6)</td>
<td>0.0036</td>
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<tr>
<td>Onset ≥ 10 years</td>
<td>36%</td>
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What work-up should you do upon diagnosing morphea?

Laboratory work-up
- ANA and RF have been associated with extra-cutaneous involvement but not clinically significant.
- ANA positive in 39.5% with skin only and 51.6% with extra-cutaneous involvement
- RF positive in 13.2% with skin only and 24.3% with extra-cutaneous involvement
- Anti-ssDNA, anti-histone, and anti-chromatin have been associated with disease severity.
- No autoantibodies correlate with disease activity or predict future disease severity.

Work-up on all en coup de sabre and Parry-Romberg patients
- MRI at diagnosis even if asymptomatic.
- Repeat MRI if symptoms develop or worsen.
- EEG at diagnosis if seizures are suspected.
- Ophthalmology exam if eye complications are suspected.
Methotrexate is the standard treatment for moderate-severe morphea

- CARRA treatment plans (MTX + Steroid)
  - Methotrexate 1 mg/kg week SQ (max 25 mg) + Steroid pulse I.V. 30 mg/kg day 1 (max 1 g)
  - Methotrexate 1 mg/kg week SQ (max 25 mg) + Prednisolone 30 mg/kg day 1 (max 1 g)

- MTX + Steroid for 3 consecutive days every month for 3 months / 1st preferred regimen
- Methotrexate 1 mg/kg week SQ (max 25 mg) + Prednisolone 30 mg/kg day 1 (max 1 g)

- Start 1 mg/kg day divided BID for 2–4 weeks
- Taper to 1 mg/kg day by 8 weeks
- Taper off by 12 weeks

- Subcutaneous methotrexate is preferred (give Emla or lidocaine cream and ice the area)
- Both tablets and injection solutions can be given orally

- Minimise side effects with folic acid and Friday administration
- Folic acid 1 mg given everyday including MTX day

- Minimise lab draws and confusion for family

- Baseline FBC, U&Es, LFTs, Urine HCG

- 1/12–FBC, LFTs

- Every 3–12–FBC, LFTs

- No increased malignancy risk

- Beukelman 2012, Kok 2014

- Increased risk of opportunistic infection

- No live vaccines
- Eg. MMR, Varicella

- Give flu injection not nasal spray

Other treatment

- Mycophenolate Mofetil (MMF) is 2nd line

- Treat with systemic Rx for 2 years

- If disease relapse
  - Give 2nd course MTX

- If further relapse consider switch to MMF but no evidence to support that

Vascular anomalies

- Infantile haemangiomata
Rebound growth
- 25% rebound
- 15% of these need systemic treatment

Predictive factors
- Age at discontinuation <9moa
- Deep IH
- Female
- Head and neck
- Segmental

Infantile hemangioma (IH)
- No ECG required prior to propranolol therapy
- Check HP and HR
- No blood sugar monitoring

EKG Prior to Propranolol?
- Must have EKG with abnormal ECG
- All were allowed to be treated with Propranolol
- Canin-Sorensen et al. 2012 patients initiated on propranolol
- 1 with PHACE included
- 15% had abnormal ECG
- All were allowed to be treated with Propranolol
- 6.1% with abnormal ECG
- All were allowed to be treated with Propranolol

No blood sugar monitoring

Topical Timolol for IH
- Timolol 0.5% gel forming solution
- 2 drops twice daily if <2cm
- 2 drops twice daily if larger
- 38% had detectable blood levels
- Those with higher doses had higher levels but no difference in response rate
- Blood levels found in:
  - 44% of scalp hemangiomas but 0% of face hemangiomas
  - 33% on limbs
  - 22% on trunk

Topical Timolol - other uses
- Paronychia and pseudopyogenic granuloma in EGFR inhibitors and Capecitabine
- Complete response in 9/10
- Potential for use in isotretinoin induced pyogenic granuloma

Vascular anomalies
- Infantile hemangiomas
  - Segmental infantile hemangiomas
  - PHACE risk
  - LUMBAR risk

Infantile haemangiomas: PHACE
- 30% chance of PHACE in hemangiomas >5 cm
- Complete PHACE workup
  - AV/IVH head and neck
  - ECHO
  - Eye exam

Topical Timolol for Paronychia and Pseudopyogenic Granulomas in Patients Treated With Epidermal Growth Factor Receptor Inhibitors and Capecitabine
- Complete response in 9/10
- Potential for use in isotretinoin induced pyogenic granuloma
**Updated consensus criteria**

- All infants with large segmental IH located on the face or scalp
- PHACE should be considered with 1 major criterion of PHACE and a large segmental haemangioma of the neck, upper trunk, or trunk and proximal upper extremity
- 2 major criteria of PHACE (eg supranumerary raphe and coarctation of the aorta) but lacking cutaneous IH

**Beyond the highest risk group...**

- S2 and parotid IH are lower risk
- ? Partial work up
- Eye
- ECHO
- ? MRI/MRA

**Cerebrovascular risk**

- Concerns re propranolol in at risk patients of possibly providing CNS ischaemia/stroke
- The reality:
  - Risk is probably very low
  - Most patients with PHACE need propranolol therapy to manage their haemangiomas
  - Need to risk stratify their CNS arteriopathy

**LUMBAR Syndrome**

- MRI (not US) with or without contrast needed for adequate exam of spine
- Renal US or other evaluations not standardised
- Depends on clinical setting

**Vascular anomalies**

- Infantile haemangiomas
  - Segmental infantile haemangiomas
    - PHACE
    - LUMBAR
- Congenital haemangiomas

**Congenital haemangiomas - RICH and NICH**

- GNAQ & GNA11 somatic mutations
- RICH
  - GLUT 1-ve, WTI-ve (Wilms tumor 1 gene)
  - Regress between 6/12 and 14/12
  - Get a transient coagulopathy
- NICH
  - More extensive
  - Can regress prior to birth
Congenital Haemangiomas

- PHCH
- Partial regression over 12/12
- Stabilisation and persistence
- Surgery required

Vascular Anomalies

- Infantile Haemangiomas
- Segmental Infantile Haemangiomas
- PHACE risk
- LUMBAR risk
- Congenital Haemangiomas
- Multifocal Lymphangioendotheliomatosis with Thrombocytopenia (MLT)

Multifocal Lymphangioendotheliomatosis with Thrombocytopenia: Presentation of Two Cases Treated with Sirolimus

- Relatively newly described vascular anomaly with thrombocytopenia
- Multiple red brown plaques and papules often with central pallor
- Clinically significant GI/Pulmonary haemorrhage - MTS mortality
- Responds well to sirolimus
- If not able to use buccal administration can lead to therapeutic serum levels

Kaposiform Haemangioendothelioma & Tufted Angiomas

- Avoid platelet transfusions
- Cryoprecipitate and platelet transfusions can be considered when procedure/intervention
- Be wary of Reye’s Syndrome – probably not an issue at doses we use
- Stop aspirin at times of vaccinations

Vascular Anomalies

- Infantile Haemangiomas
- Segmental Infantile Haemangiomas
- PHACE risk
- LUMBAR risk
- Congenital Haemangiomas
- Multifocal Lymphangioendotheliomatosis with Thrombocytopenia
- Kaposiform Haemangioendothelioma & Tufted Angiomas

Vascular Stains

- PWS and SWS
- Stains +/- overgrowth
- Geographic stains
- CM- AVM

Tufted Angioma & KHE Spectrum

- Consider platelet or cryoprecipitate transfusions
- Be wary of Reye’s Syndrome - probably not an issue at doses we use
- Stop aspirin at times of vaccinations
Port Wine Stain: Extra-cutaneous complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>PWS location</th>
<th>Work up / Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Forehead</td>
<td>Symptomatic: Neurology evaluation; Asymptomatic: Consider MRI after 6-12 months; Consider EEG; Discuss with Neurology</td>
</tr>
<tr>
<td>Ocular</td>
<td>Periocular</td>
<td>Regular Ophthalmology evaluation</td>
</tr>
<tr>
<td>Oral</td>
<td>Lower face</td>
<td>Dental evaluation; ENT evaluation</td>
</tr>
<tr>
<td>Speech</td>
<td></td>
<td>Assess for symptoms of depression, anxiety and psychosocial complications</td>
</tr>
</tbody>
</table>

PWS of Sturge-Weber Syndrome patients

- 11/66 patients with upper facial PWS had SWS
- Forehead confers risk - most not classic V1

PWS - Treatment

- Pulsed-dye laser is considered the gold standard therapeutic modality
- Treatment at a younger age leads to higher rates of clearance, reduced number of treatments and lower incidence of hypertrophy and complications
- Rapamycin (sirolimus) has been shown to have anti-angiogenic effects
- When used in combination with pulsed-dye laser, rapamycin (off-label use) may enhance the treatment efficacy in part by preventing revascularization after laser injury

Widespread blotchy stains with overgrowth

- Proportionate rather than progressive overgrowth
- SCAD: diffuse capillary malformation with overgrowth
- If large head and/or digital anomalies: MDT evaluation; Genetics consult; Consider somatic gene testing; Neuro evaluation; Consider brain MRI

Widespread stains minus worrisome features

- If lower extremity involvement: serial leg measurements until growth completed
- If >1-2 cm refer to orthopedics
- If no worrisome features: Initial 6-12 months; Thereafter annually
Geographic Stains
- All borders more sharply demarcated
- Frequent presence or development of blebs
- Less blanchable than bluish PWS
- Suggest lymphatic disease
- Signs of PIK3CA overgrowth spectrum (PROS)?
  - KTS - Klippel Trenaunay Syndrome
  - MCAP - Mehdani-Costenoble
  - CLOVE Syndrome - Congenital Lipomatous overgrowth, vascular malformation and epidermal naevi
  - FAH - Fibroadipose hyperplasia
  - FAO – Fibroadipose overgrowth

Multifocal Stains: Approach
- Always ask about family hx
- Most (~90%) CM-AVM due to mutations in RASA1
- Autosomal dominant
- 10% risk of spinal or brain AVM
- Genetic referral/testing
- Imaging of brain and spine - when and how often unclear

CM-AVMs
- AD, Variable expressivity, including intra-familial variability
- 30% have dW: Cranial, spinal, peripheral (Parkes Weber)
- +/- Lymphatic anomalies
- 50% missense germinal mutation in RASA
- Somatic second hit demonstrated in tissue
- EDNRB mutation
- ATRX mutations (encoding MEK 1)

New in Therapeutics: AVM
- Steroids in AVM not effective
- Steroids-Eluting Stent

Non-scarring alopecia
2.5 mg/mL triamcinolone acetonide for limited, patchy alopecia areata involving less than 50% of the scalp.

- Minimizes local side effects of skin atrophy and telangiectasia and likely reduces the potential for systemic adrenal suppression.
- Allows for injection of a greater volume, increasing the maximal treatment area.

Platelet rich plasma (PRP)

- PRP may have the ability to induce a longer disease remission.
- Patients treated with PRP appeared to regrow pigmented hairs from the beginning of hair regrowth compared with 25% if treated with TAC.
- Non-standardized treatment protocols and methods for assessing response make it challenging to adequately assess the potential benefit of the treatments.

Alopecia Areata - JAK inhibition

- JAK inhibition
  - If you respond, you respond well
  - Higher doses sometimes necessary
  - Relapses may occur
- Well tolerated
- Weight gain
- Eyebrows respond well
- Scalp not great

Alopecia Areata - Nail involvement

- Nail involvement in 7-65% of patients with AA
- 2 patients successfully treated with JAK inhibitor Tofacitinib
- 1/3 stopped Tofacitinib with no recurrence of nail dystrophy

Biotin - no evidence

Diffuse alopecia - supplements

<table>
<thead>
<tr>
<th>Vitamin/Mineral</th>
<th>Deficiency level</th>
<th>Daily supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>&lt; 8 mg/dL</td>
<td>Oral ferrous sulfate 320mg or ferrous gluconate 325mg + 5 mg selenium (in children, 1 mg selenium) of vitamin E + vitamin D + 0.5 mg thiamine, 1000 IU</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>&lt; 30 nmol/L</td>
<td>25 BY Vitamin D + 20 mg (10 mcg) of vitamin E + 0.5 mg thiamine, 1000 IU</td>
</tr>
<tr>
<td>Zinc</td>
<td>&lt; 10 mg/dL</td>
<td>Zinc gluconate 15-30 mg plus 500 mg vitamin D daily (in children, less)</td>
</tr>
</tbody>
</table>
Thank you!