

# Morphea in Children

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# Morphea (Localized Scleroderma)

- The most common form of scleroderma in children
- Estimated incidence 1:100,000 (an orphan disease)
- Characterized by discrete areas of firm, thickened, fibrotic skin.
- Subcutaneous tissue, muscle and/or bone may also be involved.

# Clinical Subtypes

## *Established Nomenclature*

- Plaque type
- Profunda
- Linear
- Pansclerotic
- En coup de sabre
- Morphea with lichen sclerosis

# Clinical Subtypes

## *Evolving Classification*

- Plaque type
- Profunda
- Linear
- Pansclerotic
- En coup de sabre
- Morphea with lichen sclerosis
- Focal
- Segmental
- Superficial
- Deep

# Presenting Signs

*121 Patients < 21*

- Dyspigmentation 42%
- “Bruise” 15%
- Erythema 12%
- Atrophy 12%
- Pruritus 6%
- other/unknown 40%

Gilliam et al. Presented at the AAD annual meeting Feb. 2007.

Data collected from UCSF/UCSD Derm/Rheum clinics, 2000-2006

# Natural History

- Progression over 1-3 years
- Gradual improvement after 3-5 years
- Lower risk
  - Cutaneous = “Superficial”
  - Plaque = “Focal”
- Higher risk
  - Subcutaneous = “Deep”
  - Linear = “Segmental”

# Risks

*Superficial (Cutaneous); Focal (Plaque)*

- Atrophy
- Hyperpigmentation



# Risks

## *Deep (“Profunda”)*

- Missed opportunity for early diagnosis/treatment
- Atrophy
- Adipose, muscle, bone involvement
- Asymmetry
- Disfigurement



# Risks

## *Segmental (“Pansclerotic”)*

- Atrophy
- Adipose, muscle, bone involvement
- Limb size asymmetry
- Disfigurement
- Arthritis



# Risks

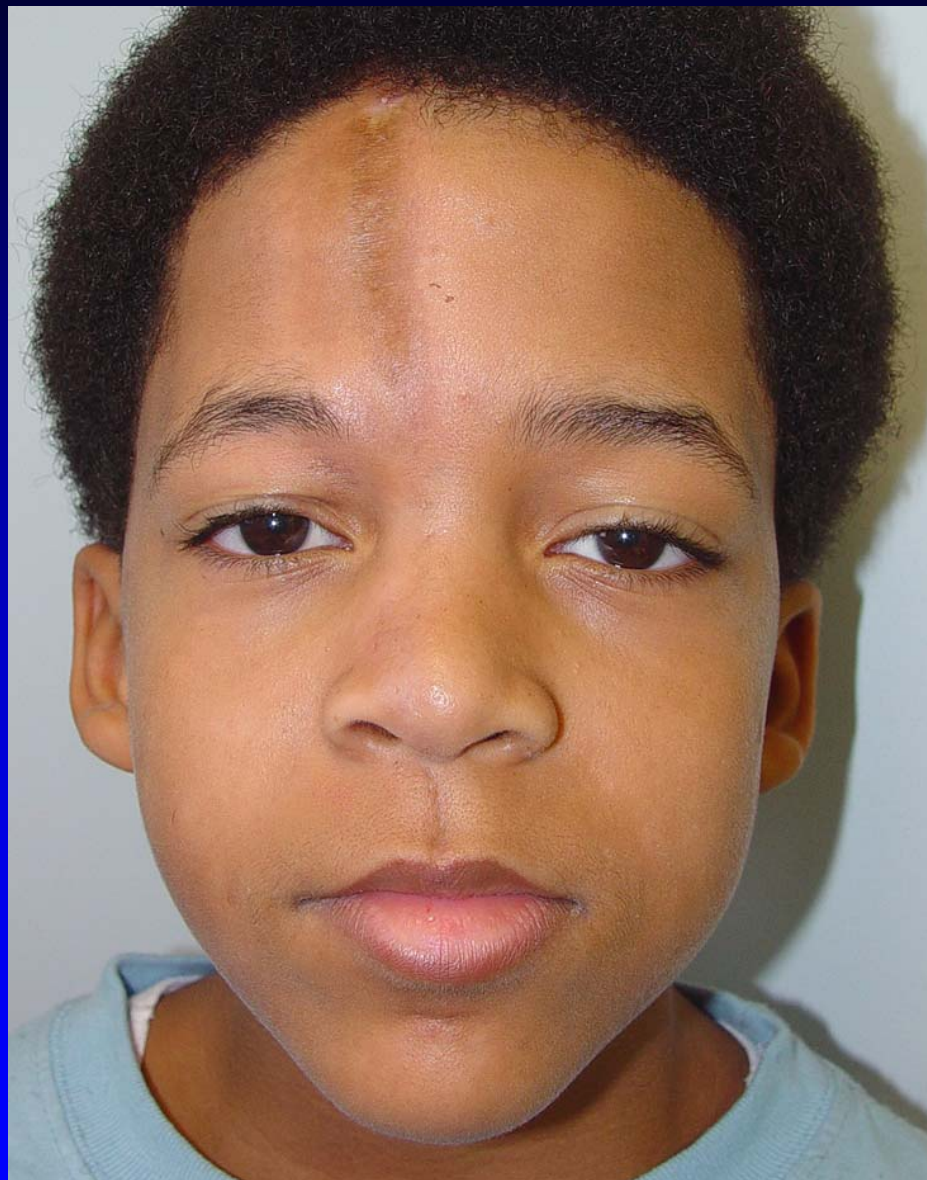
## *Segmental (“Coup de Sabre”)*

- Alopecia
- Ophthalmologic: oculomotor nerve palsy, retinal vasculitis, Iridocyclitis, uveitis, progressive endophthalmitis
- CNS
  - clinical: headache, facial palsy, meningoencephalitis, seizures
  - imaging: non-specific white matter changes, intraparenchymal calcifications, vascular malformations and aneurysms

onset morphea 1997



09/2003



01/2005



# Risks

## *Segmental, Lower Face*

- Atrophy
- Adipose, muscle, bone involvement
- Dental/orthodontal problems
- Disfigurement



# Risks

## *Lichen Sclerosus*

- atrophy
- anogenital involvement
  - pain
  - phimosis
  - encopresis
  - carcinoma
  - ?HPV



# Poor Prognostic Factors

- Segmental (Linear)
- Deep (Profunda)
- Early age of onset
- Rapid progression
- Greater surface area involvement
- Cutaneous involvement overlying a joint
- Arthritis
- Eosinophilia
- Positive serologies



# Prevalence of Autoantibodies

- ANA  
40% skin only, 52% with extracutaneous involvement
- ssDNA - 30-50%
- Histone - 40-50%
- RF  
13% skin only, 24% with extracutaneous involvement
- Cardiolipin - 15-20%
- dsDNA - <5%
- Scl-70 - <5%
- Centromere - <3%

Data from the Juvenile Working Group of the Pediatric Rheumatology European Society (PRES): Zulian et al. Arthritis Rheum 2005; 52: 2873-2881.

# Management:

## *First line therapy for low risk lesions*

- Class I topical corticosteroid monotherapy
- Topical corticosteroids plus
  - calcipotriene (Dovonex, Taclonex)  
(calcipotriene ointment no longer available)
  - tazarotene (Tazorac)
  - tretinoin/hydroquinone (Triluma)
- Imiquimod

Dytoc M, Ting PT, Man J, Sawyer D, Fiorillo L. First case series on the use of imiquimod for morphea. *Br J Dermatol.* 2005; 153:815.

# Imiquimod

- Canadian case series
- Initial 2 pts treated 1 side only, with ipsilateral improvement
- Rationale:  
induction of IFN- $\gamma$   $\rightarrow$  inhibition of TGF- $\beta$   
(which plays a role in fibrosis)
- N = 12
- Age 6-77
- Plaque-type
- TIW-QHS applications
- 6 months duration
- Clinical improvement in erythema and dyspigmentation
- Histologic improvement in dermal thickness (N = 4)

# Management:

High risk lesions require more aggressive treatment.

# Important Parameters

- Timing
- Subtype
- Location, Location, Location

# Important Parameters

- Timing – young age, ASAP
- Subtype – segmental, deep
- Location, Location, Location – face, joint-associated

# Aggressive Treatment Options

- Penicillamine
- PUVA
- Hydroxychloroquine
- NBUVB
- Methotrexate plus pulsed corticosteroids
- **Methotrexate alone**

# Assessing Improvement

## *Reliable Parameters Have Not Been Defined*

- Clinical features
  - Inspection (dyspigmentation, sclerosis. atrophy)
  - Palpation
  - Serial photography
- Skin biopsy
- Serologies
- Investigational imaging
  - 13 MHz Ultrasound
  - Infrared Thermography
  - Fluorodeoxyglucose-positron emission tomography

Bendeck SE, Jacobe HT. *Dermatol Ther* 2007; 20(2): 86.

Cosnes et al *Br J Dermatol* 2003; 148:724-9.

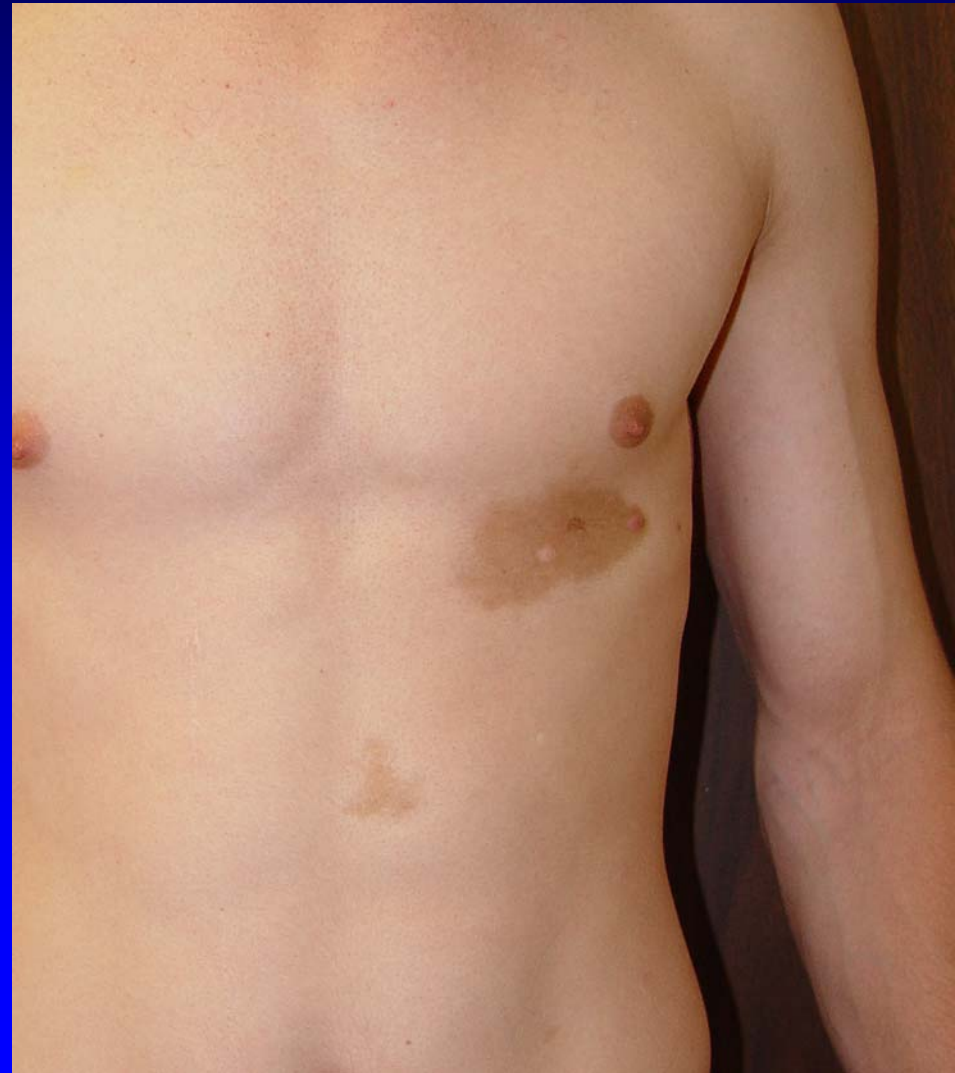
Martini et al. *Rheumatol* 2002; 41:1178-82.

# Clinical Improvement *Inspection*

Sclerotic



Hyperpigmented, atrophic



# Clinical Improvement

## *Serial Photography*



# Clinical Improvement

## *Serial Photography*



# Methotrexate

Methotrexate (MTX) competitively inhibits the enzyme dihydrofolate reductase and decreases circulating cytokines thought to be involved in the pathogenesis of scleroderma (IL-2 , IL-6, IL-8)

# Methotrexate

## *Dosing and Administration*

- 0.5 mg/kg/wk
  - single dose
  - Q12<sup>o</sup> X 3
  - QD X 3 - 4
- Possibly more well tolerated in children
  - Nausea, anorexia (13%)
  - Stomatitis
  - Hypersensitivity
  - No hepatotoxicity or pneumonitis in JRA
- Monthly labs: CBC, LFTs X 3, then Q 3mo
- Liver biopsy for high risk patients
  - obese
  - alcohol use
- Liquid dosing precaution-25 mg/cc

# Methotrexate Monotherapy for Pediatric Localized Scleroderma

## *Patient Demographics*

- N= 15
- 10 girls, 5 boys
- 14 Caucasian, 1 African-American
- Median age at dx = 10.7 yr (2.4 - 17.3)
- Median dz duration at dx = 8.5 mo (1.5 - 48)

Tom W, Obadiah J, Moore T, Siegfried E. Methotrexate Monotherapy for Pediatric Localized Scleroderma. Presented at the AAD annual meeting Feb. 2007.

# Prior Failed Treatments

| Treatment                | # Pts |
|--------------------------|-------|
| Topical corticosteroids  | 9     |
| IV/PO corticosteroids    | 3     |
| Calcipotriene ointment   | 3     |
| 0.1% Tacrolimus ointment | 1     |
| Penicillamine            | 2     |
| Hydroxychloroquine       | 3     |
| PUVA                     | 1     |

Median disease duration at MTX initiation = 11.5 mo (1.5 – 48)

Tom W, Obadiah J, Moore T, Siegfried E. Methotrexate Monotherapy for Pediatric Localized Scleroderma. Presented at the AAD annual meeting Feb. 2007.

# Methotrexate Monotherapy

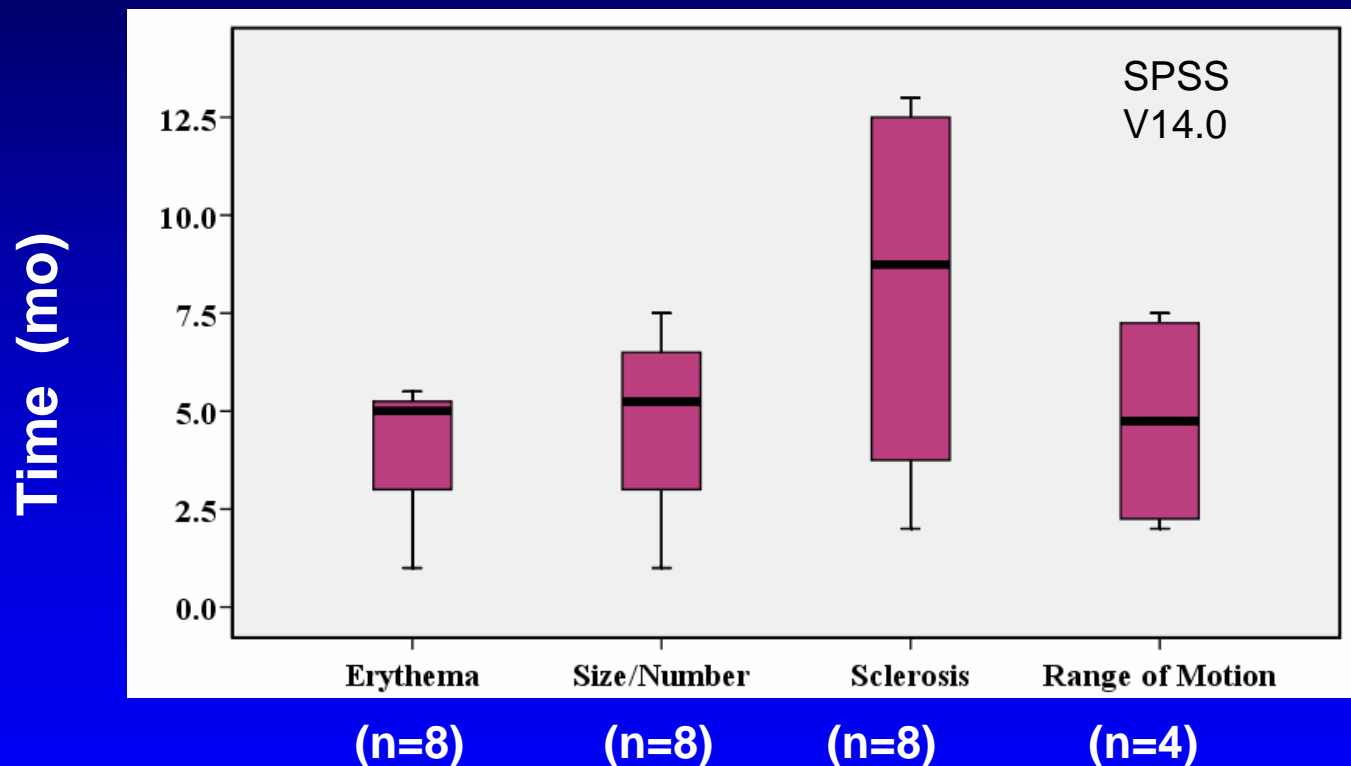
## *Therapeutic Response*

- 12 of 15 (80%) with sustained improvement ( $\geq 5$  months)
- Median duration of follow-up = 18.8 mo (6 - 49)
- Dosing –
  - Initial: 7.5 - 15 mg/wk (0.2-0.6 mg/kg/wk; mean = 0.33)
  - Max: 12.5 – 35 mg/wk (0.2-0.75 mg/kg/wk; mean = 0.46)
  - For doses  $\leq 20$  mg, MTX was taken PO
  - For doses  $> 20$  mg, MTX was given SQ to optimize absorption

Tom W, Obadiah J, Moore T, Siegfried E. Methotrexate Monotherapy for Pediatric Localized Scleroderma. Presented at the AAD annual meeting Feb. 2007.

# Time to Improvement by Lesion Characteristic

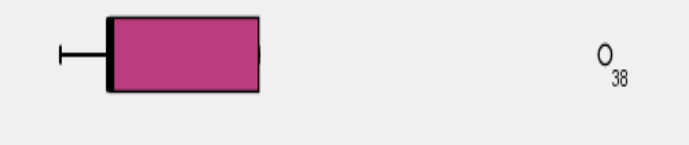

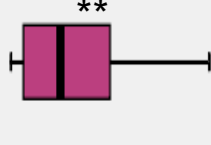
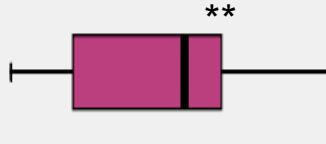
## *Responders*



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# Comparison with Other Studies

| Study        | Therapy (MTX dose)                   | Response                                | Time to Response  |
|--------------|--------------------------------------|---|---|
| Uziel et al. | MTX + IV steroids (0.3-0.6 mg/kg/wk) | 9/10 responders<br>1/10 non-responders  |    |
| Fitch et al. | MTX alone (0.3-1.0 mg/kg/wk)         | 5/5 responders<br>0/5 non-responders    |    |
|              | MTX+ PO steroids (0.4-1.0 mg/kg/wk)  | 10/12 responders<br>2/12 non-responders |    |
| Current      | MTX alone (0.2-0.75 mg/kg/wk)        | 12/15 responders<br>3/15 non-responders |  |

\*\* P= 0.03 (Mann-Whitney, SPSS V14.0), other comparisons not significant

0.00 2.00 4.00 6.00 8.00 10.00 12.00 14.00  
Months

# CONCLUSIONS

- MTX monotherapy can improve morphea in children
- Response to MTX monotherapy is comparable to combination MTX + oral/IV corticosteroids
  - Time to improvement may be a little longer but outcomes are similar
  - Side effects are fewer, dosing is simpler

Uziel Y, Feldman BM, Krafchick BR, et al. Methotrexate and corticosteroid therapy for pediatric localized scleroderma. *J Pediatr* 2000; 136: 91-5.

Fitch PG, Rettig P, Burnham JM, et al. Treatment of pediatric localized scleroderma with methotrexate. *J Rheumatol* 2006; 33: 609-14

Laxer RM and Zulian F. Localized scleroderma. *Curr Opin Rheumatol*. 2006; 18: 606-13.

# Conservative treatment for low risk lesions.

- Focal
- Superficial
- Older children
- Slow progression
- No evidence of extracutaneous involvement

# Aggressive treatment for children with higher risk factors.

- Segmental
- Deep
- Early age of onset
- Rapid progression
- Overlying a joint
- Arthritis
- Eosinophilia
- Positive serologies