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AAD Highlights 2018: Morphoea Vascular Anomalies Alopecia

15/03/18

Dr Siobhan McCarthy

Morphoea

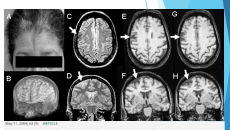
Morphoea

- 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 ECDS 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



Neuroimaging findings in scleroderma *en coup de sabre*

Neurological Manifestations

- 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

Pediatric Dermatology Vol. 29 No. 6 738–746, 2012

A Significant Proportion of Children with Morphea En Coup De Sabre and Parry-Romberg Syndrome Have Neuroimaging Findings

Yvonne E. Chin, M.D.,* Sheetal Vora, M.D.,† Eun-Kyung M. Kwon, B.A.,* and Mohit Maheshwari, M.D.‡

*Division of Pediatric Dermatology, Department of Dermatology, Medical College of Wisconsin, Milwaukee, Wisconsin, †Division of Rheumatology, Department of Pediatrics, Medical College of Wisconsin, Milwaukee, Wisconsin, ‡Division of Pediatric Radiology, Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin

Neurological Manifestations

- Mayo Clinic experience (88 adults and children)
  - 72 patients were evaluated by neurology
    - 40% had neurologic abnormalities
    - 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

Neurology
January 2015, Volume 57, Issue 1, pp 21–34 | Cite as

CNS imaging findings associated with Parry–Romberg syndrome and en coup de sabre: correlation to dermatologic and neurologic abnormalities

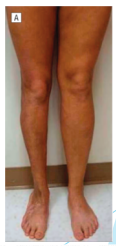
Authors Authors and affiliations

Derrick A. Doolittle, Vance T. Lehman, Kara M. Schwartz, Lily C. Wong-Kisiel, Julia S. Lehman, Megha M. Tollefson

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

Musculoskeletal manifestations

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



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

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

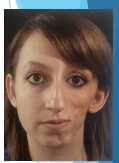
	Risk of Extracutaneous Manifestations	Odds Ratio (95% CI)	p-value
Linear morphea	38%	22.3 (2.8 – 178)	0.0035
Plaque morphea	3%		
Onset < 10 years	36%	10.0 (2.1 – 47.6)	0.0036
Onset ≥ 10 years	5%		

What work-up should you do upon diagnosing morphoea?

- 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**

What work-up should you do upon diagnosing morphoea?

- 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



What work-up should you do upon diagnosing morphoea?

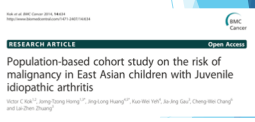
- Perform joint exams on all patients with linear morphoea on the limb
  - Joint exam at each visit
  - Physical therapy if functional limitations
  - Leg length x-ray if limb length discrepancy

Methotrexate is the standard treatment for moderate-severe morphoea

- CARRA treatment plans (MTX + Steroid)
  - Methotrexate 1 mg/kg/week SQ (max 25 mg) + Methylprednisolone 30 mg/kg/dose IV (max 1000 mg)
    - **Methylprednisolone for 3 consecutive daily doses a month for 3 months (* preferred regimen)**
    - Methylprednisolone once a week for 12 weeks
  - Methotrexate 1 mg/kg/week SQ (max 25 mg) + prednisone PO
    - Start 2 mg/kg/day divided BID for 2-4 weeks
    - Taper to 1 mg/kg/day by 8 weeks
    - Taper off by 12 months
  - Subcutaneous methotrexate is preferred (give Emla or lidocaine cream and ice the area)
  - Both tablets and injection solution can be given orally

Methotrexate is the standard treatment for moderate-severe morphoea

- Minimise side effects with folic acid and Friday administration
  - Folic acid 1mg given everyday including MTX day
- Minimise lab draws and confusion for family
  - Baseline FBC, U&E, LFTs, Urine HCG
  - 1/12 - FBC, LFTs
  - Every 3/12 - FBC, LFTs
- No increased malignancy risk
  - Beukelman 2012, Kok 2014


BMC Cancer

RESEARCH ARTICLE Open Access

Population-based cohort study on the risk of malignancy in East Asian children with Juvenile idiopathic arthritis


Research Article | Pediatric Rheumatology

Disease-modifying Antirheumatic Drug Use in the Treatment of Juvenile Idiopathic Arthritis: A Cross-sectional Analysis of the CARRA Registry

TIMOTHY BEUKELMAN, SARAH RINGOLD, TREVOR E. DAVIS, ESI MORGAN DeWITT, CHRISTINA F. PELAJO, PAMELA F. WEISS and YUKIKO KIMURA

The Journal of Rheumatology September 2012, 39 (9) 1867-1874; DOI: https://doi.org/10.3899/jrheum.120110

Methotrexate is the standard treatment for moderate-severe morphoea

- Increased risk of opportunistic infection
  - Beukelman 2012
  - HSV, VZV, Herpes Zoster
- No live vaccines
  - Eg. MMR, Varicella
  - Give flu injection not nasal spray


Research Article | Pediatric Rheumatology

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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

Vascular anomalies

- Infantile haemangiomas

Pediatrics
March 2016

Rebound Growth of Infantile Hemangiomas After Propranolol Therapy

Sonal D. Shah, Eulalia Baselga, Catherine McCuaig, Elena Pope, Julien Coulie, Laurence M. Boon, Maria C. Garzon, Anita N. Haggstrom, Denise Adams, Beth A. Drolet, Brandon D. Newell, Julie Powell, Maria Teresa García-Romero, Carol Chute, Esther Roe, Dawn H. Siegel, Barbara Grimes, Ilona J. Frieden

- Rebound growth
  - 25% rebound
  - 15% of these need systemic treatment
- Predictive factors
  - Age at discontinuation <9moa
  - Deep IH
  - Female
  - Head and neck
  - Segmental

Infantile haemangioma (IH)

- No ECG required prior to propranolol therapy
  - Check BP and HR
- No blood sugar monitoring

EKG Prior to Propranolol?

MacArthur et al: 180 patients
- 43% with abnormal EKG
- ALL were allowed to be treated with Propranolol

Castelo-Soccio et al: 202 patients initiated on propranolol
- 4 with PHACE excluded
- 49 had abnormal EKG
- ALL were allowed to be treated with Propranolol

Breuer et al: 109 patients
- 6.5% with abnormal EKG
- ALL were allowed to be treated with Propranolol

(J Am Acad Dermatol 2015;72:465-72.) (Pediatric Dermatology Vol. 33 No. 6 615–620, 2016)

Topical Timolol for IH

Pediatric Dermatology Vol. 34 No. 4 458–460, 2017

Variability of Delivery of Timolol for the Treatment of Infantile Hemangiomas

JiaDe Yu, M.D.,* Tucker Koster, B.S.,* Kala Schiltz, Ph.D.,† Marcia Seefeldt, B.S.N.,‡ Brittney Bates, B.S.,‡ Katherine Mueller, B.S.,‡ and Beth A. Drolet, M.D.‡

*Section of Pediatric Dermatology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, †Division of Biostatistics, Medical College of Wisconsin, ‡Division of Pediatric Dermatology, Children's Hospital of Wisconsin, Milwaukee, Wisconsin

- Variability - inter-user and between brands
- Drops of Timolol 0.5% gel forming solution are closer to correct dose but more inter-user variability
- Gel forming solution is used by most practitioners

Safety and efficacy of topical timolol treatment of infantile haemangioma: a prospective trial

DOI: 10.1111/bjd.15865

- Timolol 0.5% gel forming solution
  - 1 drop 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 haemangiomas but 0% of face haemangiomas
  - 33% on limbs
  - 22% on trunk

Topical Timolol - other uses

Research Letter
January 2018

Topical Timolol for Paronychia and Pseudopyogenic Granuloma in Patients Treated With Epidermal Growth Factor Receptor Inhibitors and Capecitabine

Xavier Cubiró, MD[1], Sergi Planas-Ciudad, MD[1], Mª Pilar García-Muret, MD, PhD[1], et al

Author Affiliations

JAMA Dermatol. 2018;154(1):99-100. doi:10.1001/jamadermatol.2017.4120

- Paronychia and pseudopyogenic granuloma in EGFR inhibitors and Capecitabine
  - Topical Timolol 0.5% gel (Timogel)
  - Complete response in 9/10

- ? Potential for use in isotretinoin induced pyogenic granuloma

Vascular anomalies

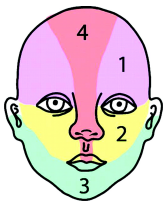
- Infantile haemangiomas
  - Segmental infantile haemangiomas
    - PHACE risk
    - LUMBAR risk

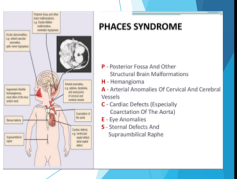
Infantile haemangiomas: PHACE

MEDICAL PROGRESS
www.jpeds.com • THE JOURNAL OF PEDIATRICS

PHACE Syndrome: Consensus-Derived Diagnosis and Care Recommendations

- 30% chance of PHACE in haemangiomas >5 cm diameter especially segments 1,3,4
- Complete PHACE workup
  - MRI/MRA head and neck
  - ECHO
  - Eye exam





PHACES SYNDROME

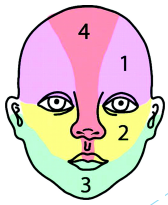
P - Posterior Fossa And Other Structural Brain Malformations
H - Hemangioma
A - Arterial Anomalies Of Cervical And Cerebral Vessels
C - Cardiac Defects (Especially Coarctation Of The Aorta)
E - Eye Anomalies
S - Sternal Defects And Supraumbilical Raphe

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 supraumbilical raphe and coarctation of the aorta) but lacking cutaneous IH

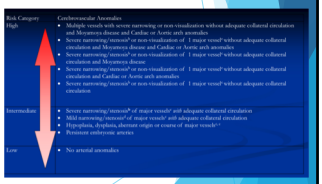
Beyond the highest risk group…

- S2 and parotid IH are lower risk
- ? Partial work up
  - Eye
  - ECHO
  - ? MRI/MRA
- Other risk settings for PHACE
  - Large periorbital IH even if not extending to S1
  - Large torso plus arm IH
  - Segmental scalp



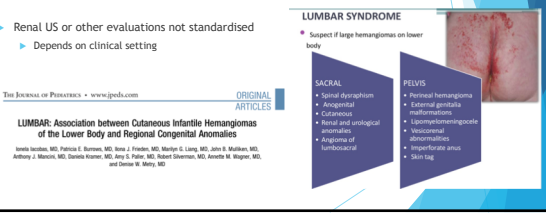
Cerebrovascular risk

- Concerns re propranolol in at risk patients of possibly provoking 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/without contrast needed for adequate exam of spine
- Renal US or other evaluations not standardised
  - Depends on clinical setting



THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

LUMBAR: Association between Cutaneous Infantile Hemangiomas of the Lower Body and Regional Congenital Anomalies

Ioreia Iacobas, MD, Patricia E. Burrows, MD, Rena J. Frieden, MD, Marilyn G. Liang, MD, John B. Mulliken, MD, Anthony J. Mancini, MD, Daniela Kramer, MD, Amy S. Paller, MD, Robert Silverman, MD, Annette M. Wagner, MD, and Denise W. Metry, MD

Vascular anomalies

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

Congenital haemangiomas – RICH and NICH

- GNAQ & GNA11 somatic mutations
- RICH
  - GLUT 1 –ve, WT1 +ve (Wilms tumor 1 gene)
  - Regress between 6/12 and 14/12
  - Get a transient coagulopathy
  - Can regress prior to birth

Pediatric Dermatology Vol. 32 No. 3 321–326, 2015

Rapidly Involuting Congenital Hemangioma with Fetal Involution

Sheilagh Maguiness, M.D., Lily Changchien Ulbiein, M.D., Marilyn G. Liang, M.D., Harry Kozakewich, M.D., and John B. Mulliken, M.D.
Boston Children's Hospital, Boston, Massachusetts

REPORT

Somatic Activating Mutations in *GNAQ* and *GNA11* Are Associated with Congenital Hemangioma

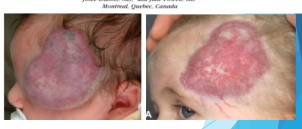
Ugur M. Ayturk,[1,2,3] Javier A. Couto,[1,2] Steven Hann,[1] John B. Mulliken,[1,2] Kaitlin L. Williams,[1] August Yue Huang,[1,2] Steven J. Fishman,[1,2] Theresia K. Boyd,[1] Harry P.W. Kozakewich,[1,4] Joyce Bischoff,[1,2] Attn K. Greene,[1,2] and Matthew L. Warman[1,2,3,5]

Congenital haemangiomas

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

Partially involuting congenital hemangiomas: A report of 8 cases and review of the literature

Eiman Nasseri, MD,[a] Maryam Piram, MD, MPH,[a] Catherine C. McCuaig, MD,[a] Victor Kokta, MD,[b] Josée Dubois, MD,[a] and Julie Powell, MD[a]
Montreal, Quebec, Canada



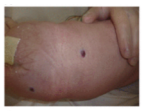
Vascular anomalies

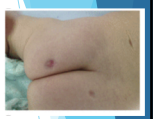
- Infantile haemangiomas
  - Segmental infantile haemangiomas
    - PHACE risk
    - LUMBAR risk
- Congenital haemangiomas
- **Multifocal Lymphangioendotheliomatosis with Thrombocytopenia (MLT)**

Pediatric Dermatology Vol. 33 No. 4 e235–e239, 2016

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

Agustina Lanoel, M.D.,* Adriana Natalia Torres Huamaní, M.D.,* Aurora Folle, M.D.,† María Josefina Sala, M.D.,‡ Mariana Alvarez, M.D.,‡ and Andrea Bettina Cervini, M.D.*
*Departments of *Dermatology, †Hematology, and ‡Pathology, Hospital de Pediatría "Prof. Dr. Juan. P. Garrahan", Buenos Aires, Argentina*





- Relatively newly described vascular anomaly with thrombocytopenia
- Multiple red brown plaques and papules often with central pallor
- Clinically significant GI/Pulmonary haemorrhage - 65% mortality

- Responds well to sirolimus
- If not able to eat buccal administration can lead to therapeutic serum levels

Novel Route of Sirolimus Administration in a Neonate

Ashley B. Clark, PharmD , Indira Chandrasekar, MD , Jennee Nickleson, PharmD

First Published April 26, 2017 | Research Article | Check for updates

Vascular anomalies

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

Tufted angioma & KHE spectrum

THE JOURNAL OF PEDIATRICS • www.jpeds.com WORKSHOP/SYMPOSIUM SUMMARY

Consensus-Derived Practice Standards Plan for Complicated Kaposiform Hemangioendothelioma

Beth A. Drolet, MD[1], Cameron C. Trenor, III, MD[2], Leonardo R. Brandão, MD[3], Yvonne E. Chiu, MD[1], Robert H. Chun, MD[4], Roshni Dasgupta, MD[5], Maria C. Garzon, MD[6], Adrienne M. Hammill, MD, PhD[7], Craig M. Johnson, DO[8], Brook Tlougan, MD[9], Francine Blei, MD[10], Michele David, MD[11], Ravindhra Elluru, MD, PhD[12], Ilona J. Frieden, MD[13], Sheila F. Friedlander, MD[14], Ionela Iacobas, MD[15], John N. Jensen, MD[16], David M. King, MD[16], Margaret T. Lee, MD[17], Stephen Nelson, MD[18], Manish Patel, DO[19], Elena Pope, MD[20], Julie Powell, MD[21], Marcia Seefeldt, RN[22], Dawn H. Siegel, MD[1], Michael Kelly, MD, PhD[23], and Denise M. Adams, MD[1]

Archetype	Suggested first-line therapy
Fulminant KHE with KMP* (neonate/young infant)	Multi-agent therapy often necessary. Consider consultation with a Vascular Anomalies Center for patient tailored recommendations.
KHE/TA with KMP*	Vincristine 0.05 mg/kg IV weekly AND prednisolone 2 mg/kg/day OR Methylprednisolone 1.6 mg/kg/day
KHE without KMP	Stable or minimally invasive lesion: Observation Lesion growth or symptoms: Prednisolone 2 mg/kg/day +/- antiplatelet therapy with aspirin 2 to 5 mg/kg/day
Symptomatic TA	Consider trial of an antiplatelet agent such as aspirin +/- ticlopidine

*Sirolimus

*Topical Sirolimus?

- 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
- KHE & tufted angiomas
- **Vascular stains**
  - **PWS and SWS**
  - **Stains +/- overgrowth**
  - **Geographic stains**
  - **CM-AVM**

Pediatric Dermatology Vol. 33 No. 6 570–584, 2016

Vascular Stains: Proposal for a Clinical Classification to Improve Diagnosis and Management

Eduardo Rozas-Muñoz, M.D.,* Ilona J. Frieden, M.D.,†,‡ Esther Roé, M.D.,* Luis Puig, M.D., Ph.D.,* and Eulalia Baselga, M.D., Ph.D.*

TABLE 2. *Clinical Patterns and Main Features of Vascular Stains*

Name of the malformation	Synonyms	Clinical characteristics	Associations	Workup
Nevus simplex	Salmon patch Angel's kiss Stork bite Fading macular stains Nevus roseus	Midline location Pink color Indistinct borders		None
Port-wine stain	Nevus flammeus	Solid stains Light red to dark purple color Persistent	SWS (only in facial PWS located over V1) Glaucoma (only in periocular PWS)	MRI in all asymptomatic children Ophthalmologic examination in all periocular PWS (every 3 months 1st year, and every 6 months second year, then annually)
Reticulated capillary malformations		Reticulated stains Poorly defined (diffuse indistinct borders) Pale pink to light red	Nonprogressive overgrowth Others: subcutaneous veins, varicosities, syndactilia, macrodactyly M-CM	Regular clinical examination Orthopedic evaluation in cases with severe limb discrepancy
Geographic stains		Very sharply demarcated borders Geographic shapes (like map of a country) Typically dark red–purple, but occasionally paler color Often associated with overlying blebs	Capillary-lymphatic venous malformation in most cases (often called "Klippel–Trenaunay syndrome")	Varies depending on individualized evaluation: careful evaluation for overgrowth, venous and lymphatic anomalies) Orthopedic evaluation in limb overgrowth MRI with and without contrast
Capillary malformation–arteriovenous malformation		Multifocal round/oval stains Peripheral halo	Arteriovenous malformations	Consider brain and spinal MRI for patients and affected relatives
Cutis marmorata telangiectatica congenita	Congenital generalized phlebectasia Nevus vascularis reticularis Congenital phlebectasia Congenital livedo reticularis	Well-demarcated dark stains Reticulated bands Epidermal atrophy Persistent with warmth	Body asymmetry capillary malformations Glaucoma in facial stains	Opthalmological evaluation in facial lesions to rule out glaucoma
Telangiectasia		Multiple discrete vascular papules and macules with radiating finer vessels	Unilateral nevoid telangiectasia: sporadic, linear or segmental distribution Hereditary benign telangiectasia: Autosomal dominant, widespread	None

Port Wine Stain: Extra-cutaneous complications

Complication	PWS location	Work up / Evaluation
Neurologic	Forehead Paramedian Hemifacial	Symptomatic: Neurology evaluation Asymptomatic: Consider MRI after 6-12 months Consider EEG Discuss with Neurology
Ocular	Periocular (upper or lower eyelid)	Regular Ophthalmology evaluation
Oral	Lower face Perioral / oral	Dental evaluation ENT evaluation Speech
Psycho-social	Any location	Assess for symptoms of depression, anxiety and psycho-social complications

PWS of Sturge-Weber Syndrome patients

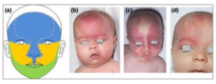
- 11/66 patients with upper facial PWS had SWS
- Forehead confers risk – most not classic V1

PAEDIATRIC DERMATOLOGY — BJD British Journal of Dermatology

New vascular classification of port-wine stains: improving prediction of Sturge–Weber risk

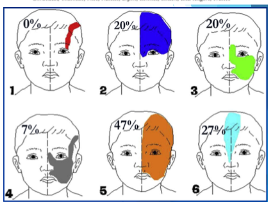
R. Waelchli,[1] S.E. Aylett,[2,3] K. Robinson,[2] W.K. Chong,[4] A.E. Martinez[1] and V.A. Kinsler[1,5]

[1]Department of Paediatric Dermatology, [2]Department of Neurosciences and [4]Department of Paediatric Neuroradiology, Great Ormond Street Hospital for Children, London WC1N 3JH, U.K.
[3]Neurosciences Unit and [5]Clinical and Molecular Genetics Unit, UCL Institute of Child Health, London, U.K.



A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain

Anne-Sophie Dutkiewicz, MD,[a,j] Khaled Ezzedine, MD, PhD,[a,j] Juliette Mazereeuw-Hautier, MD, PhD,[b] Jean-Philippe Lacour, MD, PhD,[c] Sébastien Barbarot, MD, PhD,[d] Pierre Vabres, MD, PhD,[e] Juliette Miquel, MD,[f] Xavier Balguerie, MD,[g] Ludovic Martin, MD, PhD,[h] Franck Boralevi, MD, PhD,[a,j] Pierre Bessou, MD,[i] Jean-François Chateil, MD, PhD,[i] and Christine Léauté-Labrèze, MD,[a,j] on behalf of the Groupe de Recherche Clinique en Dermatologie Pédiatrique
Bordeaux, Toulouse, Nice, Nantes, Dijon, Rennes, Rouen, and Angers, France



PWS - Treatment

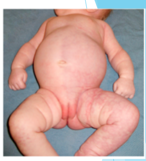
- Pulsed-dye laser is considered the gold standard therapeutic modality
  - Treatment at a younger age leads to higher rates of clearance, reduced number of treatments and lower incidence of hypertrophy and complications
- Rapamycin (sirolimus) has been shown to have anti-angiogenic effects
  - When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

Widespread blotchy stains with overgrowth

- If proportionate rather than progressive overgrowth
  - DCMO: Diffuse capillary malformation with overgrowth

Diffuse capillary malformation with overgrowth: A clinical subtype of vascular anomalies with hypertrophy

Margaret S. Lee, MD, PhD,[a] Marilyn G. Liang, MD,[a] and John B. Mulliken, MD[b]
Boston, Massachusetts



- 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 orthopaedics
- If no worrisome features
  - Initial f/u 3-6 months
  - Thereafter annually

Geographic stains

- All borders more sharply demarcated
- Frequent presence or development of blebs
- Less blanchable than blotchy PWS
- Suggest lymphatic disease

- Signs of PIK3CA overgrowth spectrum (PROS)?
  - KTS - Klippel Trenaunay Syndrome
  - MCAP - Megalencephaly-CM
  - 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 RASA-1
  - 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 AVM: Cranial, spinal, peripheral (Parkes-Weber)
- +/- Lymphatic anomalies

- 50% missense germinal mutation in RASA
- Somatic second hit demonstrated in tissue
- EPHB4 mutation
- MAP2K1 mutations (encoding MEK 1)


Capillary Malformation–Arteriovenous Malformation, a New Clinical and Genetic Disorder Caused by *RASA1* Mutations

CASE REPORTS

EPHB4 Mutation Implicated in Capillary Malformation–Arteriovenous Malformation Syndrome: A Case Report

ORIGINAL RESEARCH ARTICLE

Germline Loss-of-Function Mutations in EPHB4 Cause a Second Form of Capillary Malformation-Arteriovenous Malformation (CM-AVM2) Deregulating RAS-MAPK Signaling

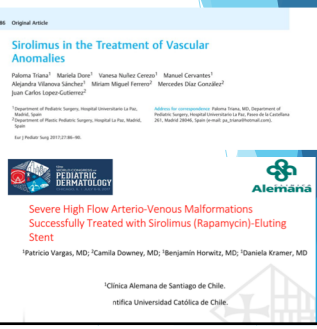
REPORT

Somatic *MAP2K1* Mutations Are Associated with Extracranial Arteriovenous Malformation

New in therapeutics: AVM

- Sirolimus in AVM not effective

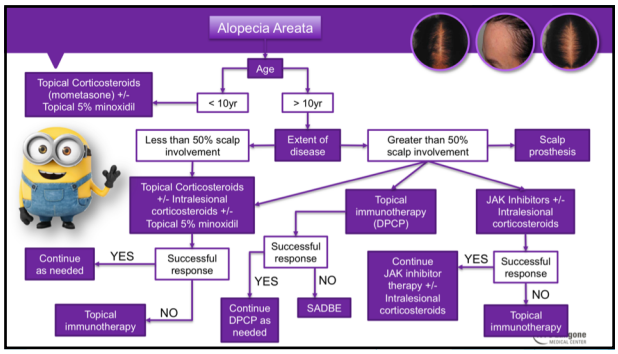
- Sirolimus-Eluting Stent


Sirolimus in the Treatment of Vascular Anomalies

Severe High Flow Arterio-Venous Malformations Successfully Treated with Sirolimus (Rapamycin)-Eluting Stent

Alopecia

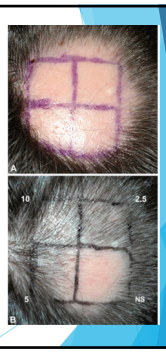
Non-scarring alopecia



Benefit of different concentrations of intralesional triamcinolone acetonide in alopecia areata: An intrasubject pilot study

http://dx.doi.org/10.1016/j.jaad.2015.04.049

- 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

CONCISE COMMUNICATION
British Journal of Dermatology

A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata

A. Trink,[1] E. Sorbellini,[1] P. Bezzola,[1] L. Rodella,[2] R. Rezzani,[2] Y. Ramot[3] and F. Rinaldi[1]

PMCID: PMC4502475

Platelet-rich Plasma as a Potential Treatment for Noncicatricial Alopecias

Glikeri Maria-Angeliki, Kouskoukis Alexandros-Efstratios, Rigopoulos Dimitris,[1] and Kouskoukis Konstantinos

- 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 those treated with TAC
- Non-standardised treatment protocols and methods for assessing response make it challenging to adequately assess the potential benefit of the treatments

Alopecia Areata - JAK inhibition

Inhibiting Janus kinases to treat alopecia areata

Sherrie J Divito & Thomas S Kupper

Alopecia areata is an immune-mediated, nonscarring form of hair loss. A new study using human clinical samples and a mouse model demonstrates that CD8α$^+$NKG2D$^+$ T effector memory cells mediate alopecia areata in part through Janus kinase (JAK) signaling and that alopecia areata might be treated with JAK inhibitors.

BG Craiglow and BA King
Oral Tofacitinib Reverses Alopecia Universalis

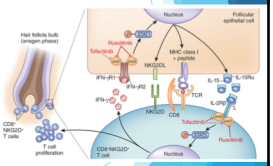
Killing Two Birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis

Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Luzhou Xing[1,2], Zhenpeng Dai[1,2], Ali Jabbari[1,2], Jane E Cerise[1,3], Claire A Higgins[2], Weijuan Gong[2], Annemieke de Jong[2], Sivan Harel[2], Gina M DeStefano[2,4], Lisa Rothman[2], Pallavi Singh[2], Lynn Petukhova[1], Julian Mackay-Wiggan[2], Angela M Christiano[1,2,5] & Raphael Clynes[2,3,6]

Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata

Milene Kennedy Crispin,[1] Justin M. Ko,[1] Brittany G. Craiglow,[1,2] Shufeng Li,[1] Gautam Shankar,[1] Jennifer R. Urban,[1] James C. Chen,[1,2] Jane E. Cerise,[1] Ali Jabbari,[1] Marten C.G. Winge,[1] M. Peter Marinkovich,[1] Angela M. Christiano,[2,3] Anthony E. Oro,[1] and Brett A. King[1]



Alopecia Areata - JAK inhibition

ORIGINAL ARTICLES

Tofacitinib for the treatment of severe alopecia areata and variants: A study of 90 patients

Lucy Y. Liu, BA,[a] Brittany G. Craiglow, MD,[a,b] Feng Dai, PhD, MS,[a] and Brett A. King, MD, PhD[a]
New Haven, Connecticut

Tofacitinib for the treatment of alopecia areata and variants in adolescents

Brittany G. Craiglow, MD,[a,b] Lucy Y. Liu, BA,[a] and Brett A. King, MD, PhD[a]
New Haven, Connecticut

Observation
April 2016
Topical Ruxolitinib for the Treatment of Alopecia Universalis

Brittany G. Craiglow, MD[a], Daniel Tavares, PharmD[b], Brett A. King, MD, PhD[a]

Research letter

Tofacitinib 2% ointment, a topical Janus kinase inhibitor, for the treatment of alopecia areata: A pilot study of 10 patients

Lucy Y. Liu BA,[a] Brittany G. Craiglow MD,[b] Brett A. King MD, PhD[a]

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

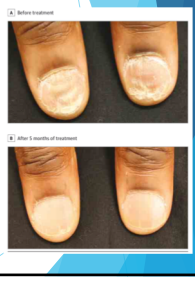
Alopecia Areata - Nail involvement

Observation
April 2016

Tofacitinib Citrate for the Treatment of Nail Dystrophy Associated With Alopecia Universalis

Arjun Dhayalan, BS[1], Brett A. King, MD, PhD[2]

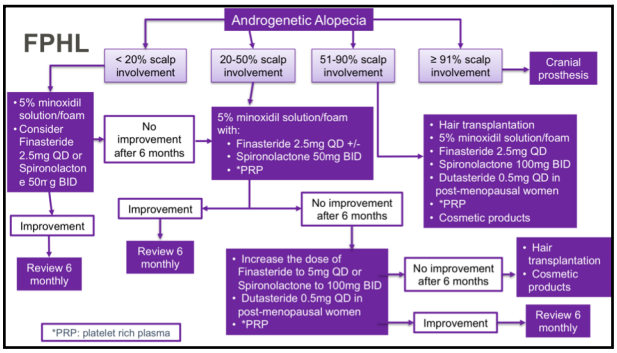
- Nail involvement in 7-65% of patients with AA
- 3 patients successfully treated with JAK inhibitor Tofacitinib
- 1/3 stopped Tofacitinib with no recurrence of nail dystrophy

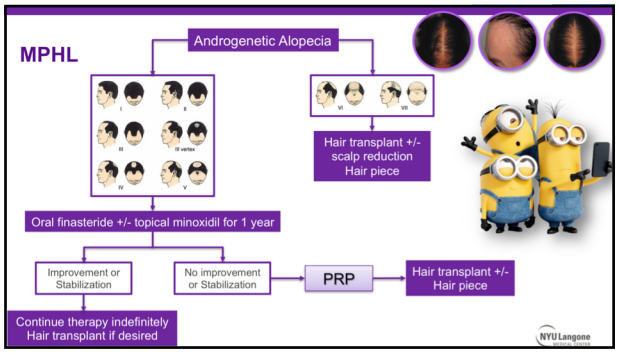


Diffuse alopecia - supplements

- Biotin - no evidence

Vitamin/Mineral	Screening lab	Deficiency level	Daily supplementation
Iron	Serum Ferritin	< 40ng/mL	Oral ferrous sulfate 325mg or ferrous gluconate 324mg x 3 months (then re-check level
Vitamin D	Serum 25-hydroxyvitamin D	< 30nmol/L	**25-hydroxyvitamin-D < 20nmol/L**: 50.000IU of vitamin D3 weekly x 6-8 weeks, then 1000 IU daily thereafter **25-hydroxyvitamin-D < 21-30nmol/L**: OTC vitamin D supplements at 1000 IU daily
Zinc	Plasma zinc level	< 60mcg/dL	Zinc gluconate 15-30mg//dayx 3 months (then re-check level)


FPHL
Androgenetic Alopecia
< 20% scalp involvement
20-50% scalp involvement
51-90% scalp involvement
≥ 91% scalp involvement
Cranial prosthesis
• 5% minoxidil solution/foam
• Consider Finasteride 2.5mg QD or Spironolacton e 50m g BID
No improvement after 6 months
5% minoxidil solution/foam with:
• Finasteride 2.5mg QD +/-
• Spironolactone 50mg BID
• *PRP
• Hair transplantation
• 5% minoxidil solution/foam
• Finasteride 2.5mg QD
• Spironolactone 100mg BID
• Dutasteride 0.5mg QD in post-menopausal women
• *PRP
• Cosmetic products
Improvement
Review 6 monthly
Improvement
Review 6 monthly
No improvement after 6 months
• Increase the dose of Finasteride to 5mg QD or Spironolactone to 100mg BID
• Dutasteride 0.5mg QD in post-menopausal women
• *PRP
No improvement after 6 months
• Hair transplantation
• Cosmetic products
Improvement
Review 6 monthly
*PRP: platelet rich plasma


MPHL
Androgenetic Alopecia
Hair transplant +/- scalp reduction Hair piece
Oral finasteride +/- topical minoxidil for 1 year
Improvement or Stabilization
No improvement or Stabilization
PRP
Hair transplant +/- Hair piece
Continue therapy indefinitely Hair transplant if desired
NYU Langone


Thank you!