Vascular Anomalies: Hemangiomas and more

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Head of Pediatric Dermatology
University Children’s Hospital, Zurich
1. Classification
2. Hemangiomas
3. Some vascular malformations
ISSVA – Classification of Vascular Anomalies

**Vascular Tumors**
- Benign
  - Infantile hemangioma
  - Congenital hemangioma (RICH, NICH, PICH)
  - Tufted angioma
  - Pyogenic granuloma
- Locally aggressive or borderline
  - Kapos. Hemangioendothelioma
- Malignant

**Vascular Malformations**
- Simple
  - Capillary malformation
  - Lymphatic malformation
  - Venous malformation
  - Arteriovenous malformation
- Combined
- Associated with other anomalies

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*Dasgupta R, Fishman SJ. ISSVA Classification. Semin Pediatr Surg 2014*
Clinical clues for diagnosis

To ask the right questions:
1. Present at birth? When first noticed?
2. Changes over time?
3. Pain?
4. Any similar lesions in the family?

Clinical examination:
1. Macule or raised / with swelling? Hot?
2. Multiple lesions? Other birthmarks?
3. Symmetry: midline lesion?
ISSVA – Classification of Vascular Anomalies

Vascular Tumors

Benign
- Infantile hemangioma
- Congenital hemangioma (RICH, NICH, PICH)
- Tufted angioma
- Pyogenic granuloma

Locally aggressive or borderline
- Kapos. Hemangioendothelioma

Malignant

Vascular Malformations

Simple
- Capillary malformation
- Lymphatic malformation
- Venous malformation
- Arteriovenous malformation

Combined
- Of major vessels
- Associated with other anomalies

## ISSVA classification of vascular tumors

<table>
<thead>
<tr>
<th>Benign vascular tumors</th>
<th>Locally aggressive or borderline vascular tumors</th>
<th>Malignant vascular tumors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infantile hemangioma / Hemangioma of infancy</td>
<td>Kaposiform hemangioendothelioma</td>
<td>DD Fibrosarcoma, Rhabdomyosarcoma, DFSP</td>
</tr>
<tr>
<td>Congenital hemangioma</td>
<td>Retiform hemangioendothelioma</td>
<td>DD Myofibroma, Fibrosarcoma, Rhabdomyosarcoma</td>
</tr>
<tr>
<td>Rapidly involuting (RICH) *</td>
<td>Papillary intralymphatic angioendothelioma (PILA), Dabska tumor</td>
<td></td>
</tr>
<tr>
<td>Non-involuting (NICH)</td>
<td>Composite hemangioendothelioma</td>
<td></td>
</tr>
<tr>
<td>Partially involuting (PICH)</td>
<td>Kaposi sarcoma</td>
<td></td>
</tr>
<tr>
<td>Tufted angioma * °</td>
<td>Others</td>
<td></td>
</tr>
<tr>
<td>Spindle-cell hemangioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epithelioid hemangioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyogenic granuloma (aka lobular capillary hemangioma)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### DD Myofibroma, Fibrosarcoma, Rhabdomyosarcoma

### DD Fibrosarcoma, Rhabdomyosarcoma, DFSP
Infantile hemangiomas

- 1 of 15 all infants affected
- unique biology (GLUT1-positiv)
- some risk factors
- pathogenesis?
  1. Somatic mutation of hemangioma stem cells
  2. Placental theory
  3. Hypoxia-induced proliferation

Chen TS. Pediatrics 2013
Greenberger S. Brit J Dermatol 2013
# Infantile hemangiomas

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Different types</th>
</tr>
</thead>
<tbody>
<tr>
<td>focal</td>
<td>superficial</td>
</tr>
<tr>
<td>multifocal</td>
<td>deep</td>
</tr>
<tr>
<td>segmental</td>
<td>mixed (superficial + deep)</td>
</tr>
<tr>
<td>indeterminate</td>
<td>reticular / abortive / minimal growth</td>
</tr>
<tr>
<td></td>
<td>others</td>
</tr>
</tbody>
</table>
Infantile hemangioma: growth pattern

- in 50% precursor lesions at birth!
- 80% of definite size reached at 3 months (cave: deep lesions)
- spontaneous involution between 2 and 4 years
- appr. 15% need therapy

Tollefson MM. Pediatrics 2012
Spontaneous involution
(mainly between age 2-4 years)

30 to 65% of infantile hemangioma leave residual changes
permanent skin changes and psychosocial impact of hemangioma residua
are increasingly appreciated
LUMBAR Syndrome (PELVIS / SACRAL)

- Lower body hemangioma
- Urogenital anomalies
- Myelopathy
- Bony deformities
- Analorectal malformations
- Renal anomalies
PHACES Syndrom

P  posterior fossa anomalies
H  hemangioma (plaque-type, face, neck, trunk, extremity) > 5 cm
A  arterial anomalies (cerebrovascular, neck, aorta)
C  cardiac anomalies
E  eye abnormalities
S  sternal defects

MRA head&neck
Echocardiography
Ophthalmology
TSH
Propranolol 1st-line treatment

Schiestl, Weibel, Eur J Pediatr 2011
## Systemic treatment options for IH other than betablockers

<table>
<thead>
<tr>
<th>Method</th>
<th>Reasons/concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Not recommended</strong></td>
<td></td>
</tr>
<tr>
<td>Interferon therapy</td>
<td>Serious side effects in infants (25% spastic diplegia)</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Haematological side effects and risk of peripheral neuropathy</td>
</tr>
<tr>
<td><strong>Potentially useful</strong></td>
<td></td>
</tr>
<tr>
<td>Corticosteroids (OCS)</td>
<td>• Monotherapy in case of propranolol intolerance</td>
</tr>
<tr>
<td></td>
<td>• Low dose in combination with propranolol for PHACES syndrome</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>• Anti-angiogenic effects potentially useful</td>
</tr>
<tr>
<td></td>
<td>• Potential side effects (e.g., on regular angiogenesis in infants) unknown</td>
</tr>
<tr>
<td></td>
<td>• No RCT yet available</td>
</tr>
</tbody>
</table>
Treatment of infantile hemangiomas today

- major challenge today is the identification of which hemangiomas require treatment and which can be left to involute spontaneously to identify hemangiomas at risk early!
- approximately 15% need therapy
- today lower threshold for treatment than a few years ago
- permanent skin changes and psychosocial impact of hemangioma residua have increasingly been appreciated

Liang MG, Frieden IJ. Semin Pediatr Surg 2014
### Hemangiomas at risk

<table>
<thead>
<tr>
<th>Level of risk</th>
<th>Clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Trunk, arms, and legs (in areas covered by clothing) &lt; 5 cm</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Segmental &gt; 5 cm trunk, arm, and leg</td>
</tr>
<tr>
<td></td>
<td>Body folds (neck, perineum, and axillae)</td>
</tr>
<tr>
<td></td>
<td>Lateral face, scalp, hands, and feet</td>
</tr>
<tr>
<td>High</td>
<td>Face—prominent dermal thickening or central facial</td>
</tr>
<tr>
<td></td>
<td>Periorbital, perinasal, and perioral</td>
</tr>
<tr>
<td></td>
<td>Segmental &gt; 5 cm face</td>
</tr>
<tr>
<td></td>
<td>Segmental &gt; 5 cm lumbosacral/perineum</td>
</tr>
</tbody>
</table>

Systemic or topical treatment?

Liang MG, Frieden IJ. Semin Pediatr Surg 2014
Current data...

*A randomized, controlled trial of oral propranolol in infantile hemangioma.*

*Treatment of infantile haemangiomas: recommendations of a European expert group.*

**Swiss Guidelines for the treatment of infantile hemangiomas with propranolol**

*in press PAEDIATRICA April 2016*
Most rapid growth: between 5.5 and 7.5 weeks

- at birth
- 2 weeks
- 4 weeks
- 6 weeks
- 8 weeks
- 2.5 months

Referral for therapy: at 4 weeks

Need for quick appointments and teledermatology!

Tollefson MM. Pediatrics 2012
Hoeger P. Eur J Pediatr 2015
Treatment with propranolol today

Where and by whom?

- "prescribers should be experienced in vascular anomalies and in evaluation young children"

- "treatment should be initiated only in clinical settings equipped and qualified for the safe and immediate management of any adverse event, in particular cardiovascular events"

Hemangiol® is licensed and reimbursed in CH

Drolet et al, Pediatrics 2013
Hoeger P. Eur J Pediatr 2015
Contraindications for propranolol treatment

- age < 4 weeks (except rapidly growing, life/function threatening IH)
- potential drug interactions
- bronchial asthma
- AV-block II° to III°, sick sinus syndrome
- bradycardia, hypotension
- cardiac failure
- proneness to hypoglycemia
- phaeochromocytoma
- Raynaud‘s syndrome
**Propranolol treatment for IH**

<table>
<thead>
<tr>
<th>Step</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pre-treatment checks</strong></td>
<td>history, clinical exam, +/- ECG, HR, BP, photo</td>
</tr>
<tr>
<td><strong>treatment start</strong></td>
<td>in-patient: age &lt; 8 weeks (correct. age), weight &lt; 3.5kg, comorbidities, social issues otherwise out-patient setting</td>
</tr>
<tr>
<td><strong>monitoring</strong></td>
<td>HR and BP 1 and 2 h after first dose and each dose increase; HR 1x/month thereafter</td>
</tr>
<tr>
<td><strong>dose / - intervall</strong></td>
<td>2 (3) mg/kg/d in 2 (3) doses/day after feeding</td>
</tr>
<tr>
<td><strong>treatment duration</strong></td>
<td>min. 6 months, often longer (12 mths or longer)</td>
</tr>
<tr>
<td><strong>stop of treatment</strong></td>
<td>no dose tapering needed, sometimes advised, further follow up needed (relapse 15%)</td>
</tr>
</tbody>
</table>
Side effects of propranolol treatment

<table>
<thead>
<tr>
<th>Very common (&gt;10 %)</th>
<th>Common (1 to 10 %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchitis</td>
<td>Bronchiolitis, bronchospasm, slightly decreased BP</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Nightmares, irritability, somnolence</td>
</tr>
<tr>
<td>Diarrhoea, vomiting</td>
<td>Constipation, acrocyanosis/cold extremities</td>
</tr>
</tbody>
</table>

Propranolol treatment should be interrupted in case of poor oral intake and intercurrent obstructive bronchitis
Side effects of propranolol treatment

Sleep disorders, bronchitis/wheezing...

- propranolol crosses the blood-brain barrier
- long-term follow-up studies are needed with respect to neuro-development
- there is no evidence to date of any long-term issues from its use in cardiology
- hydrophilic beta blockers such as nadolol and atenolol seem to be as effective for IH with less central nervous side effects and atenolol with less risk of bronchitis

Pope E. Br J Dermatol 2013
Bernabeu-Wittel J. Pediatr Dermatol 2015
Topical Timolol: Evidence for Efficacy and Degree of Systemic Absorption.

Weibel L1,2, Barysch MJ2, Scheer HS1, Königs I3, Neuhaus K4,5, Schiestl C4,5, Rentsch k6, Müller DM7, Theiler M1,2.

- 40 infants (<35 weeks old); small proliferating IH: median size 3cm²
- Timolol-Gel 0.5% 2x daily
Topical Betablockers for IH

- Increasing experience with topical timolol 0.5%
- Effective for the treatment of superficial and small hemangiomas
- Great potential for early therapy if appropriate!
- Cave: systemic absorption in young babies, large hemangiomas, large ulceration!
small superficial IH may be treated with topical betablockers (timolol)

ulcerations benefit from oral or topical betablockers; severe ulcerations may benefit from additional laser treatment (PDL)

surgical excision is indicated for disfiguring residua or exophytic IH

laser treatment (PDL) is ideal to treat residual erythema/telangiectasia in the involuted phase
Pyogenic granuloma (Botryomycoma)

- Lobular capillary hemangioma (GLUT1 negative)
- Rapid growth, bleeds easily
- Infants and toddlers
- Treatment: excision with histology; pulsed dye laser, cryotherapy
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**Vascular Tumors**

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- Congenital hemangioma (RICH, NICH, PICH)
- Tufted angioma
- Pyogenic granuloma

**Locally aggressive or borderline**
- Kapos. Hemangioendothelioma
- Tufted Angioma

**Malignant**
- usually not present at birth
- early growth phase
- present at birth at max. size

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*Dasgupta R, Fishman SJ. ISSVA Classification. Semin Pediatr Surg 2014*
Congenital vascular tumor

Most important investigation?

- full blood count (platelets)
- coagulation screen incl D-dimers and fibrinogen

Cave: Kasabach-Meritt phenomenon!

Ultrasound Doppler
Congenital hemangioma

- **RICH**
  - Rapidly involuting congenital hemangioma

- **NICH**
  - Non involuting congenital hemangioma

- **PICH**
  - Partially involuting congenital hemangioma

- Usually *not* associated with marked coagulopathy
- GLUT1 negative
- Warm to touch
- Highly vascularized („high-flow“ on early ultrasound)
- Propranolol without effect (and usually not needed)
RICH (rapidly involuting congenital hemangioma)

- Marked spontaneous involution within the first 6 months of life (and thereafter)
- Decrease of vascularization
- Residua: some discoloration, lipoatrophy
Kasabach-Meritt Phenomenon (KMP)

- profound thrombocytopenia (platelet trapping within the tumor)
- raised D-dimers
- low fibrinogen

Kaposiform Hemangioendothelioma (KHE)

Tufted angioma (TA)
Kaposiform hemangioendothelioma with Kasabach-Meritt Phenomenon (KMP)

• infiltrative vascular tumor of endothelial and lymphatic derivation
• usually presents in infancy: enlarging vascular tumor with KMP
• on extremities associated with disabling fibrosis and contractures
• surgical resection often impossible
• treatment of choice today: sirolimus

Drolet. J Pediatr 2013
Tufted angioma
+ / - Kasabach-Meritt Phenomenon (KMP)

- congenital or appear within first 5 years of life
- solitary solid firm pink-red-purple lesion
- tenderness, hypertrichosis, hyperhidrosis
- histology indicated
- may resolve spontaneously -> „watch & wait“ strategy
- aspirin, surgical excision; sirolimus
Capillary malformation (port wine stain, nevus flammeus)

The NEW ENGLAND JOURNAL of MEDICINE

Sturge–Weber Syndrome and Port-Wine Stains Caused by Somatic Mutation in GNAQ

• 1 of 300 newborns affected
• malformation of dermal capillaries and venules

Shirley MD. N Engl J Med, Mai 2013
Sturge-Weber malformation

- Capillary malformation in *fronto-temporal* ("forehead") region
- Leptomeningeal angiomatosis
- +/- glaucoma
→ epilepsy, developmental delay, hemiparesis

Zurich: brain MRI (incl. contrast) age 3-6 months

Waelchli R. Br J Dermatol 2014
Capillary malformation: treatment of choice

Pulsed-dye laser (585nm/595nm)

Alternative: IPL, Nd:YAG

Anderson RR et al. Science 1983
Faurschou A et al. Cochrane Database Syst Rev. 2011
PDL for nevus flammeus: at what age?

Until the age of approximately 7-9 years under GA (iv-sedation)

- **Face, neck, chest:**
  start at age 10 to 12 months

- **Extremities:**
  usually start > 7-9 years under local anesthesia*

*Ametop Gel® 4%
Venous malformations

- Usually sporadic
- From birth, may be noted later
- Mucosa and skin
- Bluish swellings
- Joint- and muscle involvement

- Phleboliths, pain
- bleeding in joints
- Localized/disseminated intravasal coagulopathy!
Diagnostic test for venous malformations

Localized intravasal coagulopathy
- D-Dimers $\uparrow$
- Fibrinogen $\downarrow$

D-Dimers: Sensitivität 43%
Spezifität 96%

Ultrasound-Doppler + MRI

Dompmartin et al. Arch Dermatol 2009
Management of venous malformations

Conservative
- pain management, Compression
- Aspirine, low-molecular heparin
- Rapamycin?

Surgical
- Sclerotherapie („first-line therapy“)
- surgical resection

Lymphatic malformations (Lymphangioma)

- microcystic
- macrocystic

Complications

- Bleeding in cysts
- Infections (cellulitis)
- Disfigurement
Management of lymphatic malformations

Sclerotherapy
(zB. OK432, Ethibloc, Bleomycin or Picibanil)

Surgical excision

Laser: CO2 / pulsed dye for lymphangioma circumscripturn

Drugs: Rapamycin (Sirolimus)

Management of AVM

**Intervention:**
- $\frac{3}{4}$ of patients need treatment until adolescence
- Primary goal: to prevent progression and destruction
- Embolisation
- Resection
- Combination of 1. embolisation and 2. resection

**Drugs:** Rapamycin (Sirolimus), Thalidomid

PI3K-AKT-mTOR signalling pathway

mTOR inhibitors are a promising new treatment in vascular anomalies

**PROS** (PI3K related overgrowth syndrome)
- lymphatic malformation
- Klippel-Trenaunay syndrome
- CLOVES
- Macrocephaly-CM

PTEN hamartoma tumor syndrome

Proteus syndrome

Sirolimus

Luks et al, J Pediatrics, 2015
Summary

- Read the early signs for hemangiomas early!
  Most rapid growth of hemangioma: between 4 and 8 weeks - consider treatment early!
- Consider histology of congenital vascular tumors and know the mimickers of congenital hemangiomas
- Investigate early for Kasabach-Meritt phenomenon in congenital vascular tumors
- Capillary malformation with risk for Sturge Weber malformation - > fronto-temporal region (forget V1)!
- Multidisciplinary management for vascular malformations
Ein Nävus wird umgangssprachlich meist als "Muttermal" oder "Leberfleck" bezeichnet. Als "kongenitale melano-zytäre Nävi" bezeichnet man angeborene, braune Muttermale.

Infantile Hämangiome sind knotige Ansammlungen von Blutgefässen. Umgangssprachlich werden sie auch "Blutschwärmmchen" genannt.


Als therмische Verletzung wird eine Schädigung des Gewebes
Epidermolysis bullosa-Zentrum
Kinderspital Zürich
Seit Oktober 2015
Abteilungen für Dermatologie, Plastische Chirurgie und Wundbehandlung
Ankündigung:

Donnerstag 1. Dezember 2016 (ganztags) in Zürich

**Symposium: Zentrum Kinderhaut**

- Dermatologie
- Plastisch-Rekonstruktive Chirurgie
- Verbrennungsmedizin
- Wundbehandlung