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## DERMATOLOGY CLINIC
### What's Your Diagnosis?

## Red Forehead Plaque in an Infant

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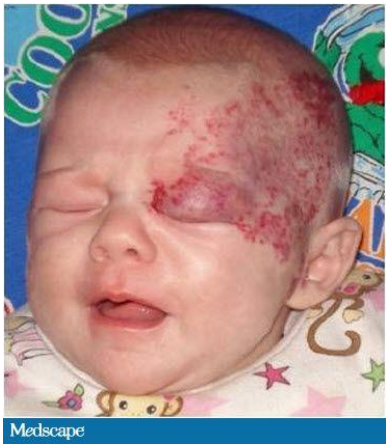
A 6-week-old female (41-year-old mother; ex-38 week GA, uncomplicated singleton pregnancy, non-forceps vaginal delivery; 2750g birth weight) presents for a well-baby check-up, and evaluation of a new red plaque on the left forehead, extending towards the orbit. It was not noticed at birth, but has been growing and becoming more raised in the last 2-3 weeks. There are no grey-white patches or ulceration on the skin surface, and there is no proptosis of the eye. The infant has never seized. She has had no cyanotic spells or feeding difficulties. She has no other skin lesions.




What should management include?

A) Oral Propranolol
B) Ophthalmology evaluation
C) Echocardiogram
D) MRI/MRA of the Head and Neck
E) All of the Above

**Answer: (E) All of the Above.** This patient has an infantile hemangioma and is at risk for PHACE(S) Syndrome.

**VASCULAR LESIONS** – Pediatric vascular lesions are classified by the type of vessels involved, as well as the growth pattern. Vascular tumors are neoplasms comprised of a specific type of blood vessel that proliferates rapidly and, in some cases, may never stop growing without intervention. Examples include: infantile hemangiomas, congenital hemangiomas (NICH, RICH) and pyogenic granulomas. On the other hand, vascular malformations are comprised of abnormal vessels of a specific type(s) that are present at birth and remain static or very slow-growing throughout life. Examples include: capillary malformations (port wine stains, 'stork bites'), venous, arterial, arterio-venous and lymphatic malformations.

***VASCULAR TUMORS***

**INFANTILE HEMANGIOMAS**

- ***Characteristics*** – Infantile Hemangiomas (IH's) are present in ~4 % of healthy babies. 75-90% are solitary lesions and are found on the head/neck. Superficial IH's are bright red, while deeper ones can have a bluish tinge. Unlike vascular malformations, IH's are not present at birth, but rather, develop within the first month of life. However, there may be a premonitory lesion at birth (hypopigmented, blanching or faint pink/purple bruise-like flat patch). The growth phase can last up to 1 year, particularly in larger IH's or those with a deeper component. Proliferation occurs between months 2-3 of life, with the most rapid growth occurring between 5-7 weeks of life. The growth phase of superficial infantile hemangiomas usually plateaus by 4-6 months of life. This is why it is important to treat early and aggressively when there is a risk of disfigurement, painful ulceration and/or loss of function. After the first year of life, the hemangioma tends to involute approximately 10% per year, so that is 90-100% resolved by age 10 years. Regression of superficial lesions is recognized by central greying/lightening. Residual skin changes (white, scar-like, saggy) can persist in up to 30% of cases and can usually be predicted by 3.5 years of age. Psychosocial impact is noted by 4 years of age. Hence, if surgery is necessary for cosmesis, it should be performed between 3-4 years of age. Risk factors for developing an IH include: female, Caucasian, prematurity, multiple gestation (twin, triplet), older maternal age, preeclampsia and placenta previa.
- ***Danger Zones*** – Hemangiomas that involve the orbit or eyelid can exert pressure on the globe, which can lead to astigmatism, proptosis, tear duct occlusion, amblyopia or blindness. Patients should be evaluated and followed by ophthalmology from infancy, and systemic treatment should be initiated, if needed. Hemangiomas that involve the 'beard zone' of the lower face and neck can be associated with airway compromise. Laryngeal hemangiomas can physically obstruct the airway, while extension around the trachea can cause external constriction of the airway. Any sign of respiratory distress, including hoarse cry, stridor or inability to feed is an emergency, and the child must be taken to the emergency room immediately for intubation. Clinically stable infants should be referred to ENT for urgent evaluation.
- ***Multiple Hemangiomas*** – Infants presenting with multiple cutaneous hemangiomas are at increased risk of having internal hemangiomas, as well, particularly on the liver. Small liver hemangiomas are usually asymptomatic, but large ones can be associated with high-output cardiac failure, internal bleeding, hypothyroidism and failure to thrive. Infants with >5 (some dermatologists argue 3) should have a screening abdominal ultrasound.

- ***Management***
    - **<u>Observation</u>** – Superficial IH's will involute with time. Most begin to regress naturally at 1 year of age, and are often barely noticeable by 10 years of age. Larger and deeper lesions can leave behind hypopigmented, atrophic patches or fibrofatty plaques, the latter of which can be managed surgically. Non-facial lesions are usually observed.
    - **<u>Skin Care</u>** - Local skin care is the same as that of normal infant skin (soap, water, moisturizers). Ulceration can be expected in ~10% of IH's. These lesions require careful cleaning, greasy ointment and non-stick dressings, as well as pain medication.
    - **<u>Topical Rx</u>** – Timolol maleate 0.5% gel-forming solution is a topical beta-blocker that can be used to slow the growth and help shrink superficial IH's. It is applied topically to the lesion 2-3 times a day for 6-12 months, or until stable improvement is achieved. There is no consensus yet on how long to treat. It is also considered to be an off-label use by the FDA. While there is a potential risk of systemic absorption in larger or ulcerated lesions and in younger, low weight infants, it is deemed safe for most patients. Patients should be fed within an hour after application of the gel, to prevent potential hypoglycemia.
    - **<u>Local/Intralesional Rx</u>** – Larger local IH's and ulcerated lesions can be treated with intralesional steroid injections, as well as pulsed-dye laser.
    - **<u>Systemic Rx</u>** – Until 2008, oral steroids were the mainstay of treatment of potentially dangerous/ulcerated/disfiguring IH's. Today, oral propranolol is the first-line, FDA-approved systemic treatment for these IH's. Appropriate cases in which propranolol might be considered include: Large or segmental facial IH; Nasal tip or ear IH; Periorbital or retrobulbar IH; Perioral, lip, tongue, intraoral or neck IH; Periorificial, if at risk for ulceration (axillary, anal); Multiple cutaneous IH with or without visceral involvement. It is recommended that treatment begin before 3 months of age, the time of greatest proliferation. It should not be started before 5 weeks of age (corrected gestational age) in infants >2kg, and can be safely initiated as an outpatient at 8 weeks of age with pre-treatment EKG and no other comorbidities. Dosing of this oral beta-blocker should start at 0.5mg/kg/day and increased by 0.5mg/kg/day every 3 doses (aka, daily) to reach 2mg/kg/day divided bid-tid, depending on the child's weight. It is generally continued for 6-12 months. Theoretically, blood pressure and heart rate should be checked 1 hour after an increase in dose, as well as bi-weekly during dose escalation, weekly for the first 4 weeks on goal dose, and then every 2 weeks (although it is usually only performed in patients at high risk for cardiac issues). Side effects of oral propranolol include: hypotension, bradycardia, bronchospasm (in children with asthma, RAD), nightmares and hypoglycemia. The latter is prevented by feeding one hour after each dose and at least every 4-6 hours overnight. Oral steroids may still be used in some cases (as adjuvant Rx, or when propranolol is contraindicated). Also, vincristine has been used in life-threatening cases that are refractory to propranolol.

- ***<u>PHACE(S) Association</u>*** – PHACES association should be considered when a large, segmental, infantile hemangioma is present on the face. There is a 30% chance of having other components of the PHACES association if the hemangioma is >20cm$^2$, and even more likely, if the IH involves more than one region of the ipsilateral face (e.g., forehead and maxilla). The PHACES components include: **P**osterior fossa malformation (usually

Dandy-Walker), **H**emangioma (facial, segmental, >5cm), **A**rterial/**A**ortic anomalies, **C**ardiac anomalies (septal defects, aortic coarctation, anomalous vessels), **E**ye abnormalities (congenital cataracts, microphthalmia, optic nerve hypoplasia), **S**upraumbilical/**S**ternal raphe. It is prudent to rule out any of these structural anomalies. These infants should have an MRI/MRA of the head/neck, an echocardiogram, and have their eyes examined by an ophthalmologist.

***VASCULAR MALFORMATIONS***

**NEVUS SIMPLEX (Capillary Malformation)**

- These are flat, salmon, pink or red patches on the eyelids, forehead or back of the head/neck ('angels kisses' and 'stork bites,' respectively) that are generally present at birth or soon afterwards. They are observed in up to 40% of babies, and they tend to fade in the first 1-2 years of life (except for the ones on the back of the head/neck). They do not grow or become thick. They are classified as capillary malformations, and are due to temporary dilatations of capillaries in the skin. There is no systemic or organ involvement. They tend to resolve on their own without medical intervention. Parental reassurance is key to management. If the pinkness persists, it can be treated with a pulsed dye laser.

**PORTWINE STAIN (PWS) (Capillary Malformation)**

- Unlike IH's, port wine stains (PWS) are always present at birth. They can be seen in up to 1/1000 newborns, and have recently been associated with a somatic mutation in the GNAQ gene. PWS can develop on the face, body or extremities, and their appearance will evolve with time; they start as pink or red flat patches at birth, which often become larger and purple with puberty, and can become thick, raised, rubbery or bumpy over time. They are categorized as capillary malformations. They are segmental, and do not involve the entire face, trunk or limb. On the face, PWS tend to localize in one of 3 regions (frontal/forehead, maxillary and mandibular). If they involve the frontal area forehead, eyelids), then they may be associated with congenital glaucoma and an ophthalmology exam is needed ASAP. If they involve bilateral forehead areas or unilateral forehead/maxillary areas, then there is a high risk of Sturge-Weber Syndrome (see below). PWS on the midline back overlying the spine can be associated with lipomas, dimples, sinuses and tethered cord. Tethered cord can become a neurological emergency. Neurological evaluation and possible ultrasound or MRI is recommended. PWS do not resolve on their own. If they are not associated with an underlying syndrome, then no treatment is necessary. The cosmetic appearance of PWS can be improved with serial laser treatments. A pulsed dye laser (PDL, 585nm-595nm) is most frequently used. Laser treatment is painful and may require general anesthesia in young children. Care of a PWS is the same as the care of the rest of the skin. The skin is intact and no special soaps, lotions or creams are necessary.

- ***STURGE WEBER SYNDROME (SWS)*** – SWS involves an extensive capillary malformation in the frontal segment of the face (forehead, eyelid, temple), eye abnormalities, brain and neurological abnormalities, including seizures. SWS is more common in females. It is also more common when the PWS occurs in bilateral frontal/forehead distribution or over ipsilateral forehead/maxillary regions (lower eyelid, malar cheek, upper white lip) regions. Immediate ophthalmologic exam with measurement of ocular pressure is recommended for infants with a frontal/forehead/eyelid PWS to rule

out congenital glaucoma. MRI for potential SWS may be considered (looking for leptomeningeal calcifications that can lead to seizures, developmental delay and hemiplegia). Consider SWS in an infant with PWS and epilepsy (seizure disorder).

- ***BECKWITH WEIDMANN SYNDROME*** (and other overgrowth syndromes) – Capillary malformations overlying the midline spine can be suggestive of Beckwith Weidmann Syndrome, if the patient has other concurrent signs, including enlarged tongue, hypothyroidism and hypertrophy.

**COMBINED VASCULAR MALFORMATION**

- ***KLIPPEL-TRENAUNAY SYNDROME (KTS)*** – KTS, aka, angio-osteohypertrophy, involves a congenital malformation of veins, capillaries and lymphatics, as well as local soft tissue overgrowth. It develops on the extremities, buttock or trunk (leg most common). Clinically, one limb is usually longer or larger than the other, and the hypertrophy is present at birth. There may be purple, compressible, venous malformation nodules and dilated vessels. Diagnosis of KTS is made in infancy or early childhood. Patients require regular monitoring to monitor function, disability and disfigurement, as well as overlying skin changes. Management involves compression stockings and surgical intervention; early orthopedic involvement is recommended for limb length discrepancies and patients should be seen in a multidisciplinary vascular lesion clinic.

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