# Capillary Malformations and Associated Syndromes

8

Megha M. Tollefson and Adrienne M. Hammill

## Abbreviations

| | |
|---|---|
| AVM | Arteriovenous malformation |
| CLOVES | Congenital lipomatous overgrowth and vascular malformation with epidermal nevus and skeletal abnormalities |
| CM | Capillary malformation |
| CMTC | Cutis marmorata telangiectatica congenita |
| CNS | Central nervous system |
| CT | Computed tomography |
| CVM | Capillary venous malformation |
| DCMO | Diffuse capillary malformation with overgrowth |
| KTS | Klippel-Trenaunay syndrome |
| M-CM | Macrocephaly-capillary malformation syndrome |
| MRA | Magnetic resonance arteriography |
| MRI | Magnetic resonance imaging |
| MRV | Magnetic resonance venography |
| PDL | Pulsed-dye laser |
| PPV | Phakomatosis pigmentovascularis |
| PWB | Port-wine birthmark |
| PWS | Port-wine stain |
| SWS | Sturge-Weber syndrome |

M. M. Tollefson
Division of Pediatric Dermatology, Mayo Clinic, Rochester, MN, USA
e-mail: Tollefson.Megha@mayo.edu

A. M. Hammill (✉)
Division of Hematology, Hemangioma and Vascular Malformation Center, University of Cincinnati College of Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
e-mail: adrienne.hammill@cchmc.org



C. C. Trenor III, D. M. Adams (eds.), *Vascular Anomalies*,
https://doi.org/10.1007/978-3-030-25624-1_8

## Capillary Malformations

### Port-Wine Birthmark

The terms capillary malformation (Table 8.1) and port-wine stain (PWS) or more recently port-wine birthmark (PWB) are often used interchangeably. PWB, also referred to as a *nevus flammeus*, is the most common type of capillary malformation. PWB occur in 0.3% of all newborns and are present at birth [1], although may initially be misdiagnosed as a bruise or other birth trauma. They are flat, well-demarcated, and usually located on one side of the body respecting the midline and

**Table 8.1** Capillary malformations and associated syndromes

| Lesion | Pattern | Associations | Prognosis | Treatment |
|---|---|---|---|---|
| Capillary malformation (CM) | Flat, well-demarcated, homogeneous | Facial/forehead involvement: Sturge-Weber syndrome | Do not fade; may darken and thicken over time | None or PDL |
| Nevus simplex | Faint, pink, characteristic locations | None | Forehead and eyelids commonly fade | None needed |
| Sturge-Weber syndrome (SWS) | Homogeneous facial capillary malformation | Glaucoma, seizures, developmental delay | Central nervous system and ophthal mologic complications | PDL for CM, appropriate subspecialty treatment of seizures and glaucoma |
| CMTC | Fixed reticulate coarse vascular pattern | Soft tissue atrophy, ulceration | Capillary malformation will often lighten with age | Rarely needed |
| DCMO | Diffuse (multiple discontinuous body regions), often reticular pattern, prominent superficial veins (1/3) | Overgrowth, possible leg length inequality | May lighten somewhat | Orthopedic referral for leg length issues as indicated |
| CVM | Capillary malformation borders less defined, venous dilation most commonly superficial veins, deep system intact | Overgrowth, possible limb length inequality | Significant coagulopathy not common | Orthopedic referral for leg length issues<br>Supportive care: compression therapy<br>Sclerotherapy, endovascular laser, or radiofrequency ablation |
| PPV | Variable clinical findings, all with capillary malformation | Variable | Variable | Laser treatment of cutaneous findings |

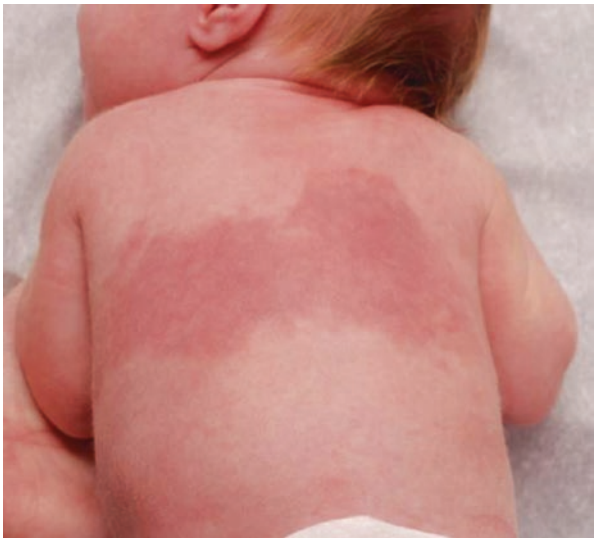

**Fig. 8.1** Capillary malformation. Well-defined capillary malformation on the trunk of a child

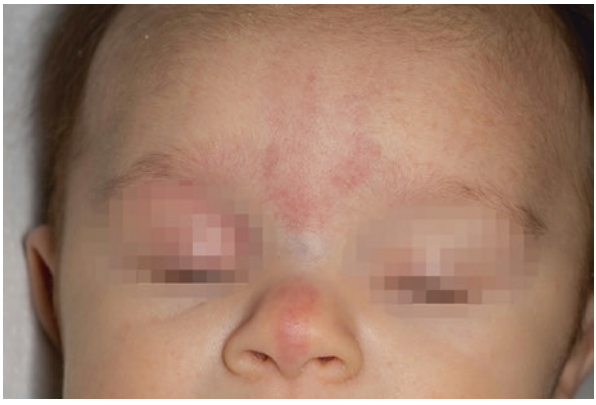

**Fig. 8.2** Glabellar and eyelid nevus simplex

grow in proportion to the child but early on may be confused for infantile hemangiomas or nevus simplex (Fig. 8.1). A somatic activating mutation in GNAQ has been found to be responsible for the development of classic PWB in both Sturge-Weber syndrome and in non-syndromic PWB. These mutations are enriched within, but not limited to, blood vessel endothelial cells in skin [2, 3] and brain [4]. In addition, mutations in the closely related GNA11 gene have been identified in some GNAQ-negative capillary malformations [5].

Unlike PWB, infantile hemangiomas undergo a rapid growth phase in early infancy, followed by gradual spontaneous resolution. Nevus simplex, also known as "stork bites" or "angel kisses," are present in 30–40% of newborns at birth, commonly involve the glabella, nape of the neck, and eyelids, and generally fade within the first 2 years of life (Fig. 8.2) [6, 7]. Some, particularly those on the nape of the

neck, may persist into adulthood. While not a true malformation, they are composed of ectatic capillaries and felt by most to be a form of persistent fetal circulation. Although faint, more salmon pink in color, and often midline, they may sometimes be mistaken for PWB, particularly when less common sites are involved. When additional sites such as the scalp, nose, lip, lumbosacral skin, and back are involved in addition to the more common sites, the term "nevus simplex complex" has been proposed [7].

A PWB may occur at any location of the body, most often on the face where they may extend to mucosal surfaces, may range in size from small to extremely large, and may be present as one patch or as multiple patches. PWB and other CMs may be associated with certain congenital syndromes, several of which will be discussed in this chapter. The appearance and location of PWB can be important when considering associations and underlying syndromes; those that have a more "geographic" appearance are more likely to be associated with underlying abnormalities particularly when involving a limb [8]. PWB present on the face may require evaluation for ocular and neurologic associations [9]. Those present in the lumbosacral area may be associated with underlying spinal dysraphism (especially when seen with another associated anomaly such as a lipoma or hair tuft), while those in the cervical area may be associated with an underlying mass or pit [10, 11]. They may be slightly warm but significant warmth on exam should suggest another diagnosis, including hemangioma or a combined malformation involving an arteriovenous malformation (AVM), as in CM-AVM.

The diagnosis of a PWB is usually a clinical one, but when biopsied or excised, histopathology shows an increased number of ectatic capillaries primarily located in the superficial dermis. There may also be impaired neural control of these blood vessels, which then leads to progressive dilation of the vessels and altered vascular flow [12]. While ultrasound evaluation is often not necessary in the diagnosis of a PWB, it can be helpful in ruling out an underlying or associated arteriovenous malformation (AVM) if one is suspected, as a PWB will show slow-flow and an AVM will have high-flow on Doppler interrogation.

PWB persist throughout life. Although benign, several complications may occur directly related to the CM. A common complication is the development of overlying dermatitis. This should be treated, especially in those undergoing treatment for the CM, and usually responds to skin-directed therapy with moisturizer and topical steroids. While initially flat and macular, PWB may darken, thicken, and become more nodular during adulthood. This can happen at any location of the body, but is more common with PWB involving the head and neck, where 2/3 develop soft tissue or bony hypertrophy or nodule formation [13, 14]. In one study of head and neck PWB, without treatment, soft tissue hypertrophy began at 9 years of age particularly when involving the mid-face. Fourteen percent of patients had associated bony hypertrophy starting at 15 years of age, and 44% developed nodules at an average of 22 years of age [14]. Treatment (discussed below) is often recommended in an effort to prevent these complications. Trunk and limb PWB may also develop thickening and hypertrophy, as well as vascular bleb formation often in association with an underlying lymphatic or venolymphatic malformation [8]. Pyogenic granulomas, benign but friable vascular tumors, may also develop within PWB and should be treated appropriately [15].

## Sturge-Weber Syndrome

Sturge-Weber syndrome (SWS), also known as encephalotrigeminal angiomatosis, is a triad first described in 1879 consisting of a facial capillary malformation, ocular vascular malformations leading to glaucoma and buphthalmos, and leptomeningeal/central nervous system (CNS) vascular malformation predisposing to seizures and developmental delay. Historically it was hypothesized that SWS is caused by a somatic mosaic mutation, and indeed whole exome sequencing from three patients with SWS confirmed a causative somatic activating mutation in GNAQ [16]. These findings were confirmed in another study that found this same GNAQ mutation in 80% of patients with sporadic SWS [17].

### Skin Manifestations

A child who has any facial PWB has up to a 6% chance of having SWS (Fig. 8.3) [18]. Historically, those with a PWB in the distribution of the trigeminal nerve, particularly V1, were felt to be at highest risk for the development of SWS, with approximately

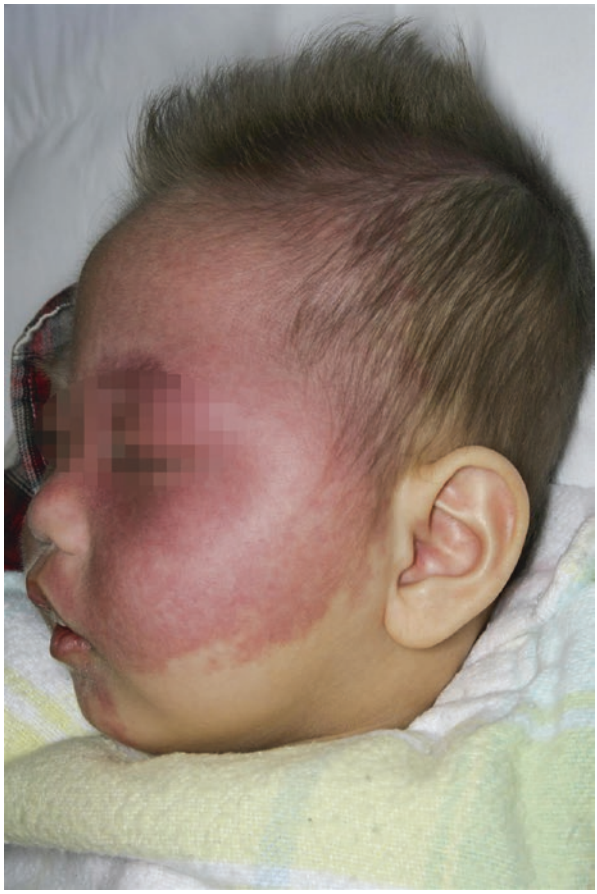

**Fig. 8.3** Facial port-wine birthmark in a patient with Sturge-Weber syndrome

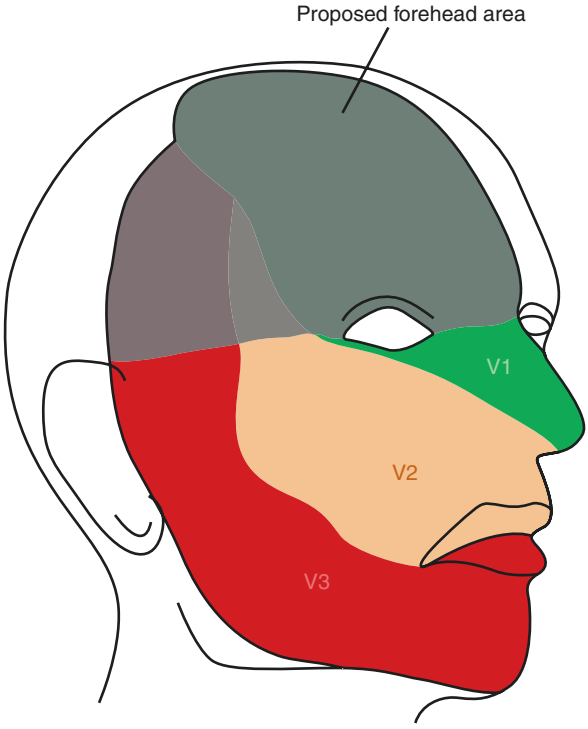


**Fig. 8.4** Forehead area at high risk for Sturge-Weber syndrome. Distribution of the "forehead," defined as any part of the forehead from the midline to an imaginary line between the outer canthus of the eye and the top of the ear including the upper eyelids. (Reused with permission from Waelchli et al. [21]; http://onlinelibrary.wiley.com/doi/10.1111/bjd.13203/full#bjd13203-fig-0001)

8% having SWS [19]. Newer studies suggest that patterns of facial PWB distribution that correspond to vascular patterns of mosaicism, especially when involving the forehead, are associated with an increased risk of SWS (Fig. 8.4) [20, 21]. Out of 192 patients with a facial PWB, when the forehead was not involved, not a single patient had seizures, abnormal neurologic development, abnormalities on MRI, nor glaucoma; in all of those who had one or more of those abnormalities, the forehead was invariably involved, with the defined forehead area involving portions of all three branches of the trigeminal nerve [21].

The CM present in SWS may extend onto mucosal surfaces and may result in gingival hypertrophy; this may be more pronounced in those with SWS being treated with phenytoin for seizures. Maxillary bone hypertrophy may also be seen, especially in those patients with overlying PWB. Macrochelia, or lip overgrowth, has recently been related to the presence of GNAQ mutation in lip [22].

## Ocular Manifestations

The most common ocular abnormality seen in SWS is glaucoma, with a prevalence of 50–60% [23]. Presence of the CM on the eyelid increases the risk for glaucoma. The precise mechanism for its development is unknown, but it is usually ipsilateral to the intraocular vascular malformation (may be bilateral

especially in those with bilateral PWB) with mechanical pressure or increased venous pressure as possible reasons. Two-thirds of patients develop glaucoma at birth or in early infancy, but the risk of development is lifelong with a mean age of diagnosis of 2.9 years; thus patients must continue to be monitored for early detection and treatment [23]. In those that are at risk, recommendations are for first ophthalmological examination in the neonatal period and if normal, then re-evaluation frequently for the first 2 years, followed by at least annually thereafter. Corneal clouding at birth is an indication of acute angle glaucoma and should be treated emergently. Those with congenital or early-onset glaucoma may develop buphthalmos.

## CNS Manifestations

Seizures are the most common neurologic manifestation of SWS, present in up to 90% of patients [24] and more common in those with bilateral PWB. Similar to glaucoma, seizures usually develop within the first year of life but may also develop later [25]. Later age of seizure onset correlates with lower prevalence of developmental delay and fewer special educational needs [26]. Developmental delay and intellectual impairment are common in patients with SWS; the underlying mechanisms appear to be multifactorial. Abnormal venous drainage can lead to venous stasis and microvascular thrombosis. Recurrent seizures, along with inappropriate autonomic response to those seizures, can lead to ischemic damage. Transient stroke-like or hemiplegia episodes have also been seen in up to 30% of patients with SWS and seem to be more common in toddlers who suffer minor head injuries [25]. Headaches are also a common complaint in patients with SWS, with 28% of patients reporting symptoms of migraine headache [27].

CNS imaging is often helpful in establishing the diagnosis and in delineating the extent of SWS, although routine imaging in infancy in the absence of neurologic symptoms has not been universally recommended as it may give false negative results before the age 1 year and the majority of infants with a facial port-wine birthmark do not have brain involvement. Contrast-enhanced MRI remains the gold standard for diagnosis of intracranial involvement because the characteristic “tram track” intracranial calcifications, visible by CT scan or plain x-ray films, often do not appear until 2 years of age or later. MRI should be performed with gadolinium contrast and should also interrogate the vascular anatomy of the brain with MRV. Susceptibility-weighted imaging and post-contrast flair provide increased sensitivity in demonstrating the extent of involvement with abnormal leptomeningeal and deep draining vessels. In addition, diffusion sequences should be performed, as well as spectroscopy if possible [28, 29]. Findings of leptomeningeal enhancement, choroid plexus enlargement, with or without venous anomalies, extensive deep draining vessels, or cortical atrophy would be consistent with a diagnosis of Sturge-Weber syndrome in an infant or young child.

Care of the patient with SWS must be multidisciplinary. Its treatment is primarily aimed at control of neurologic and ocular symptoms, though increasing attention is being paid to the role of thrombosis in the pathogenesis of SWS. Low-dose aspirin is increasingly used in these patients with some improvement in their symptoms, including seizure frequency [30, 31]. Patients should be counseled on the importance of good hydration and prompt fever control. Furthermore, because prolonged seizures worsen cerebral perfusion in SWS, aggressive seizure management is critical. Treatment options for the CM will be discussed below. Patients may also be directed to The Sturge-Weber Foundation (www.sturge-weber.com) for resources and support.

## Cutis Marmorata Telangiectatica Congenita (CMTC)

CMTC is an uncommon but clinically distinctive cutaneous vascular malformation. It is present at birth and mimics the physiologic cutis marmorata (mottling) which is commonly seen in young infants, particularly when they are cold; however, there are some distinctive distinguishing features. It may also resemble a reticular PWB. CMTC has a fixed reticulate coarse vascular pattern (Fig. 8.5) that can also be accentuated by cold, accompanied by varying amounts of telangiectasia, soft tissue atrophy, and potentially, ulceration [32, 33]. Unlike with cutis marmorata, the erythema does not resolve with warming. There may also be varying amounts of subcutaneous atrophy, particularly over joints, with resulting skin breakdown.

CMTC may be generalized but more commonly involves only one extremity (the leg in 75% of cases) and respects the midline [34]. It is most often an isolated finding but in some cases, congenital anomalies have been reported. Congenital anomalies may be associated in up to 50% of patients although that is likely an overestimation due to referral and reporting bias [34]. The most commonly

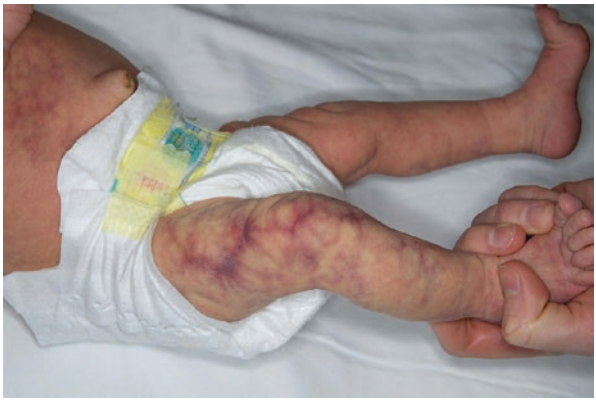

**Fig. 8.5** Cutis marmorata telangiectatica congenita. Note distinct coarse reticular pattern of the trunk and leg

associated abnormality is limb atrophy (usually the one that is affected), but other associations may include hyperplasia (overgrowth) of the limb, aplasia cutis congenita, asymmetry of the skull, macrocephaly, syndactyly, scoliosis, hypothyroidism, developmental delay, and anogenital anomalies, among others, although many of these may due to the presence of alternative diagnoses such as macrocephaly-capillary malformation (M-CM, discussed further in the Overgrowth Syndromes chapter) [35]. CMTC is seen in Adams-Oliver syndrome, which consists of limb defects and aplasia cutis congenita.

Histopathology findings in CMTC are variable but often consist of an increased number of dilated capillaries in the dermis and subcutaneous tissues. However, the diagnosis is primarily a clinical one. An etiology for the development of CMTC is unknown, although genetic mosaicism has been proposed. No active treatment is indicated in the majority of cases. CMTC usually lightens with age in the majority of patients, usually by age 2, although some residual reticulate erythema usually persists [36]. In cases of ulceration, the ulcer should be treated with supportive care.

## Diffuse Capillary Malformation with Overgrowth (DCMO)

DCMO has recently been suggested as a distinct clinical entity, in order to differentiate it from other capillary malformation overgrowth syndromes which have higher likelihoods of complications and significant morbidity [37]. Specifically, DCMO has been defined as diffuse capillary malformation, involving multiple body regions in discontinuum, and often having a reticular pattern (Fig. 8.6). It tends to lighten some with age but rarely as significantly as true CMTC. Prominent superficial veins are noted to be involved in approximately one-third of patients.

Overgrowth does not necessarily correlate with areas of CM, and growth remains proportionate throughout life. With overgrowth of one of the lower extremities, patients should be monitored for limb length inequality through puberty; 55% of patients in the initial series were found to have limb length discrepancies. Thirty percent of patients have abnormalities of the digits, including soft tissue syndactyly, "sandal gap" deformity, and macrodactyly. Of note, such abnormalities are also described in CLOVES syndrome (see Overgrowth Syndromes chapter). In addition, some patients have unilateral facial overgrowth and are frequently noted to have accelerated dental eruption on the hypertrophic side, even in the absence of any capillary malformation in the area.

No patient in the initial series of 73 had any developmental delays. There were no abdominal malignancies detected, even with 11% (7 of 73) having total hemihypertrophy. At least one patient was noted to have a Chiari I, and those patients with capillary staining crossing midline should be considered for workup of spinal anomalies.

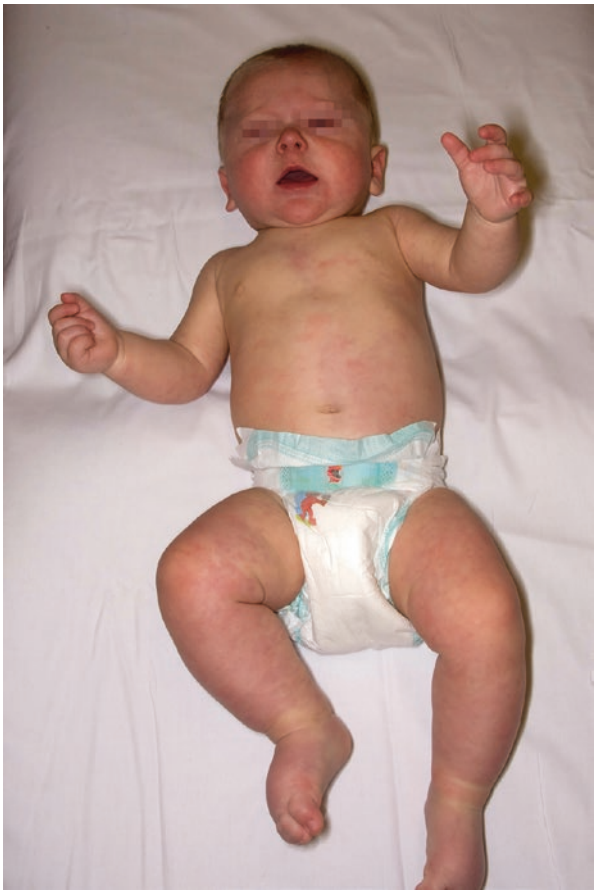

**Fig. 8.6** Diffuse capillary malformation with overgrowth

## Capillary Venous Malformation (CVM)

Capillary malformations may also be associated with venous distention. This may occur even in otherwise "simple" PWB, with increased visibility of draining veins, but is most clear in large regional capillary malformations. Venous distention becomes more visible with time and with height gain (due to an increased effect of gravity), so may not be recognized in early childhood. Many of these patients will go on to have distended and/or ectatic veins visible below the capillary malformation and sometimes even peripheral to the CM (Fig. 8.7).

These are likely distinct from malformations seen in Klippel-Trenaunay syndrome (KTS), as they do not contain any lymphatic component, and the capillary lesions tend to have less defined borders [38]. Dilation of veins occurs most commonly in superficial veins, but may also be seen in deep veins and

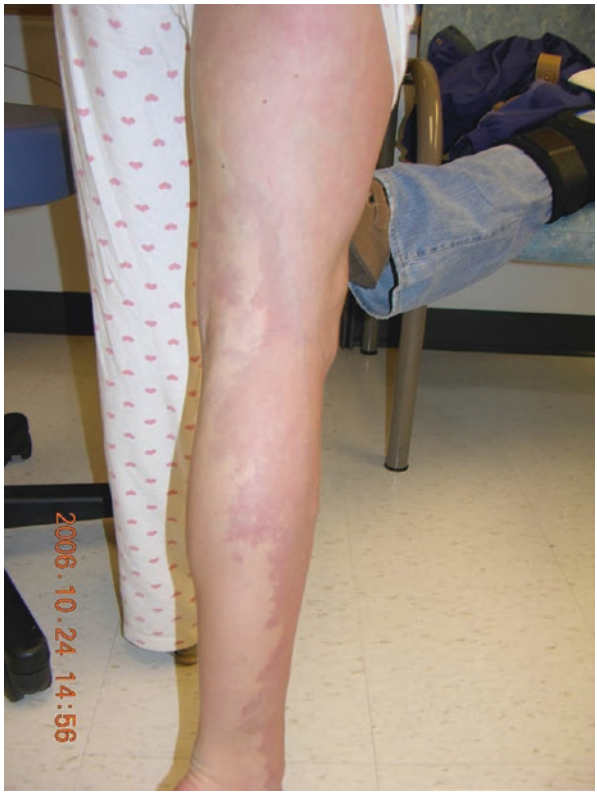


**Fig. 8.7** Capillary venous malformation

intramuscular vessels. The most frequent areas for distention are the popliteal fossa and the dorsal foot.

Venous distention becomes symptomatic in some, but not all, patients over time. This generally presents as pain within the distended veins, but has alternately been described as pressure or burning, and may be accompanied by swelling. The symptomatic distention can be treated with supportive care, including compression therapy, or with sclerotherapy. In time, endovascular laser or radiofrequency ablation may have an increasing role in these patients, as those with CVM generally have an intact deep venous system, in contrast to those with KTS (discussed further in Overgrowth Syndromes). Leg length inequality is also noted in a majority of patients, including both overgrowth and undergrowth of the involved bones. Depending on the degree of discrepancy, this can be treated with noninvasive intervention such as use of a shoe lift for the shorter leg or more invasive procedures such as epiphysiodesis of the longer limb.

Of note, this group of patients does not seem to have increased prevalence of coagulopathy, thrombophlebitis, or bleeding and thus may portend a significantly less symptomatic prognosis than for KTS.

### Phakomatosis Pigmentovascularis (PPV)

PPV is a term used to describe a group of disorders consisting of an extensive CM, along with a melanocytic or epidermal nevus. There are five types described in the classification depending on the particular findings. Extracutaneous findings, including neurologic and ocular abnormalities, may also be present [39].

- Type I: CM + epidermal nevus
- Type II: CM + dermal melanocytosis, with or without nevus anemicus (most common, accounts for 70–80% of PPV)
- Type III: CM + nevus spilus, with or without nevus anemicus
- Type IV: CM + dermal melanocytosis + nevus spilus, with or without nevus anemicus
- Type V: CMTC + dermal melanocytosis [40]

This is a rare group of disorders that are thought to be sporadic, although slightly more common in females [41]. Treatment is generally supportive, although laser treatment may be considered for the cutaneous findings.

## Treatment

Capillary malformations do not resolve spontaneously, and their persistence can be associated with a number of complications, including medical ones described above, and psychosocial difficulties [42]. The treatment of choice is the pulsed dye laser (PDL). Treatment of the CM before it begins to thicken and hypertrophy may prevent or delay thickening and nodularity later in life, and for that reason, many advocate for treatment early in childhood [43]. However, whether or not early treatment results in a better cosmetic outcome as compared to later treatment is still controversial with authors on both sides of the argument. The timing of treatment, however, must be weighed with the possible risks of general anesthesia early in life. In very young infants, treatment can sometimes be accomplished with swaddling and topical anesthetic agents alone if the CM is localized. Older children are often able to tolerate PDL with only topical anesthesia if the CM is not extensive and does not involve the eyelid.

The PDL targets intravascular hemoglobin and as a result ablates target vasculature with minimal collateral damage. Multiple treatments spaced 6–8 weeks apart are necessary. While complete clearance is generally unattainable, most treated lesions demonstrate 50 to 90% lightening, with some variation largely based on location of the lesion; the centrofacial area and limb lesions are generally less responsive to treatment possibly due to relatively increased blood vessel density and diameter [44, 45]. Maintenance treatment throughout life may be required, with repeat laser procedures as indicated.

There is a subset of CMs that are “PDL-resistant.” In these patients novel, laser and light therapies are being utilized and studied, including intense pulsed light and

the long-pulsed tunable dye, alexandrite, and Nd:YAG lasers [46]. In addition, several studies now suggest that topical sirolimus may be a helpful adjunctive treatment option in patients undergoing laser treatment for their CMs, to prevent revascularization in the immediate posttreatment period [47, 48].

In patients with visible CMs, specialty cosmetic cover-up can be used to camouflage the affected area; this has been shown to improve quality of life in affected patients [49].

## References


1. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. Pediatrics. 1976;58:218–22.
2. Couto JA, et al. Endothelial cells from capillary malformations are enriched for somatic GNAQ mutations. Plast Reconstr Surg. 2016;137:77e–82e. https://doi.org/10.1097/PRS.0000000000001868.
3. Tan W, et al. The somatic GNAQ mutation (R183Q) is primarily located within the blood vessels of port wine stains. J Am Acad Dermatol. 2016;74:380–3. https://doi.org/10.1016/j.jaad.2015.09.063.
4. Huang L, et al. Somatic GNAQ mutation is enriched in brain endothelial cells in Sturge-Weber syndrome. Pediatr Neurol. 2017;67:59–63. https://doi.org/10.1016/j.pediatrneurol.2016.10.010.
5. Couto JA, et al. A somatic GNA11 mutation is associated with extremity capillary malformation and overgrowth. Angiogenesis. 2017;20:303–6. https://doi.org/10.1007/s10456-016-9538-1.
6. Alper JC, Holmes LB. The incidence and significance of birthmarks in a cohort of 4,641 newborns. Pediatr Dermatol. 1983;1:58–68.
7. Juern AM, Glick ZR, Drolet BA, Frieden IJ. Nevus simplex: a reconsideration of nomenclature, sites of involvement, and disease associations. J Am Acad Dermatol. 2010;63:805–14. https://doi.org/10.1016/j.jaad.2009.08.066.
8. Maari C, Frieden IJ. Klippel-Trenaunay syndrome: the importance of "geographic stains" in identifying lymphatic disease and risk of complications. J Am Acad Dermatol. 2004;51:391–8. https://doi.org/10.1016/j.jaad.2003.12.017.
9. Tallman B, et al. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous system complications. Pediatrics. 1991;87:323–7.
10. Davis DA, Cohen PR, George RE. Cutaneous stigmata of occult spinal dysraphism. J Am Acad Dermatol. 1994;31:892–6.
11. Enjolras O, Boukobza M, Jdid R. Cervical occult spinal dysraphism: MRI findings and the value of a vascular birthmark. Pediatr Dermatol. 1995;12:256–9.
12. Smoller BR, Rosen S. Port-wine stains. A disease of altered neural modulation of blood vessels? Arch Dermatol. 1986;122:177–9.
13. Cordoro KM, Speetzen LS, Koerper MA, Frieden IJ. Physiologic changes in vascular birthmarks during early infancy: mechanisms and clinical implications. J Am Acad Dermatol. 2009;60:669–75. https://doi.org/10.1016/j.jaad.2008.11.020.
14. Lee JW, Chung HY, Cerrati EW, O TM, Waner M. The natural history of soft tissue hypertrophy, bony hypertrophy, and nodule formation in patients with untreated head and neck capillary malformations. Dermatol Surg. 2015;41:1241–5. https://doi.org/10.1097/DSS.0000000000000525.
15. Garzon MC, Enjolras O, Frieden IJ. Vascular tumors and vascular malformations: evidence for an association. J Am Acad Dermatol. 2000;42:275–9. https://doi.org/10.1016/S0190-9622(00)90138-5.
16. Shirley MD, et al. Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ. N Engl J Med. 2013;368:1971–9. https://doi.org/10.1056/NEJMoa1213507.

17. Nakashima M, et al. The somatic GNAQ mutation c.548G>A (p.R183Q) is consistently found in Sturge-Weber syndrome. J Hum Genet. 2014;59:691–3. https://doi.org/10.1038/jhg.2014.95.
18. Piram M, et al. Sturge-Weber syndrome in patients with facial port-wine stain. Pediatr Dermatol. 2012;29:32–7. https://doi.org/10.1111/j.1525-1470.2011.01485.x.
19. Enjolras O, Riche MC, Merland JJ. Facial port-wine stains and Sturge-Weber syndrome. Pediatrics. 1985;76:48–51.
20. Dutkiewicz AS, et al. A prospective study of risk for Sturge-Weber syndrome in children with upper facial port-wine stain. J Am Acad Dermatol. 2015;72:473–80. https://doi.org/10.1016/j.jaad.2014.11.009.
21. Waelchli R, et al. New vascular classification of port-wine stains: improving prediction of Sturge-Weber risk. Br J Dermatol. 2014;171:861–7. https://doi.org/10.1111/bjd.13203.
22. Ma G, Liu F, Cai R, Liu Y, Lin X. Somatic GNAQ mutation in different structures of Port-wine Macrocheilia. J Invest Dermatol. 2018;138:S218.
23. Sharan S, et al. Port-wine vascular malformations and glaucoma risk in Sturge-Weber syndrome. J AAPOS. 2009;13:374–8. https://doi.org/10.1016/j.jaapos.2009.04.007.
24. Paller AS. The Sturge-Weber syndrome. Pediatr Dermatol. 1987;4:300–4.
25. Lo W, et al. Updates and future horizons on the understanding, diagnosis, and treatment of Sturge-Weber syndrome brain involvement. Dev Med Child Neurol. 2012;54:214–23. https://doi.org/10.1111/j.1469-8749.2011.04169.x.
26. Comi A, Roach ES, Bodensteiner JB. In: Bodensteiner JB, Roach ES, editors.. Ch. 4, p. 69–93 Sturge-Weber Syndrome: The Sturge-Weber Foundation; 2010.
27. Cambon H, et al. Focal chronic ischemia and concomitant migraine: an atypical form of Sturge-Weber angiomatosis? Rev Neurol. 1987;143:588–94.
28. Lin DD, Barker PB, Hatfield LA, Comi AM. Dynamic MR perfusion and proton MR spectroscopic imaging in Sturge-Weber syndrome: correlation with neurological symptoms. J Magn Reson Imaging. 2006;24:274–81. https://doi.org/10.1002/jmri.20627.
29. Lin DD, Barker PB, Kraut MA, Comi A. Early characteristics of Sturge-Weber syndrome shown by perfusion MR imaging and proton MR spectroscopic imaging. AJNR Am J Neuroradiol. 2003;24:1912–5.
30. Bay MJ, Kossoff EH, Lehmann CU, Zabel TA, Comi AM. Survey of aspirin use in Sturge-Weber syndrome. J Child Neurol. 2011;26:692–702. https://doi.org/10.1177/0883073810388646.
31. Lance EI, Sreenivasan AK, Zabel TA, Kossoff EH, Comi AM. Aspirin use in Sturge-Weber syndrome: side effects and clinical outcomes. J Child Neurol. 2013;28:213–8. https://doi.org/10.1177/0883073812463607.
32. Picascia DD, Esterly NB. Cutis marmorata telangiectatica congenita: report of 22 cases. J Am Acad Dermatol. 1989;20:1098–104.
33. South DA, Jacobs AH. Cutis marmorata telangiectatica congenita (congenital generalized phlebectasia). J Pediatr. 1978;93:944–9.
34. Kienast AK, Hoeger PH. Cutis marmorata telangiectatica congenita: a prospective study of 27 cases and review of the literature with proposal of diagnostic criteria. Clin Exp Dermatol. 2009;34:319–23. https://doi.org/10.1111/j.1365-2230.2008.03074.x.
35. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations. Part II: associated syndromes. J Am Acad Dermatol. 2007;56:541–64. https://doi.org/10.1016/j.jaad.2006.05.066.
36. Enjolras O. Cutis marmorata telangiectatica congenitaAnnales de dermatologie et de venereologie. 2001;128:161–6.
37. Lee MS, Liang MG, Mulliken JB. Diffuse capillary malformation with overgrowth: a clinical subtype of vascular anomalies with hypertrophy. J Am Acad Dermatol. 2013;69:589–94. https://doi.org/10.1016/j.jaad.2013.05.030.
38. Uihlein LC, Liang MG, Fishman SJ, Alomari AI, Mulliken JB. Capillary-venous malformation in the lower limb. Pediatr Dermatol. 2013;30:541–8. https://doi.org/10.1111/pde.12186.
39. Ruiz-Maldonado R, Tamayo L, Laterza AM, Brawn G, Lopez A. Phacomatosis pigmentovascularis: a new syndrome? Report of four cases. Pediatr Dermatol. 1987;4:189–96.

40. Fernandez-Guarino M, et al. Phakomatosis pigmentovascularis: clinical findings in 15 patients and review of the literature. J Am Acad Dermatol. 2008;58:88–93. https://doi.org/10.1016/j.jaad.2007.08.012.
41. Happle R. Phacomatosis pigmentovascularis revisited and reclassified. Arch Dermatol. 2005;141:385–8. https://doi.org/10.1001/archderm.141.3.385.
42. Strauss RP, Resnick SD. Pulsed dye laser therapy for port-wine stains in children: psychosocial and ethical issues. J Pediatr. 1993;122:505–10.
43. van der Horst CM, Koster PH, de Borgie CA, Bossuyt PM, van Gemert MJ. Effect of the timing of treatment of port-wine stains with the flash-lamp-pumped pulsed-dye laser. N Engl J Med. 1998;338:1028–33. https://doi.org/10.1056/NEJM199804093381504.
44. Renfro L, Geronemus RG. Anatomical differences of port-wine stains in response to treatment with the pulsed dye laser. Arch Dermatol. 1993;129:182–8.
45. Selim MM, et al. Confocal microscopy study of nerves and blood vessels in untreated and treated port wine stains: preliminary observations. Dermatol Surg. 2004;30:892–7. https://doi.org/10.1111/j.1524-4725.2004.30259.x.
46. Savas JA, Ledon JA, Franca K, Chacon A, Nouri K. Pulsed dye laser-resistant port-wine stains: mechanisms of resistance and implications for treatment. Br J Dermatol. 2013;168:941–53. https://doi.org/10.1111/bjd.12204.
47. Marques L, et al. Topical rapamycin combined with pulsed dye laser in the treatment of capillary vascular malformations in Sturge-Weber syndrome: phase II, randomized, double-blind, intraindividual placebo-controlled clinical trial. J Am Acad Dermatol. 2015;72:151–158.e151. https://doi.org/10.1016/j.jaad.2014.10.011.
48. Nelson JS, Jia W, Phung TL, Mihm MC Jr. Observations on enhanced port wine stain blanching induced by combined pulsed dye laser and rapamycin administration. Lasers Surg Med. 2011;43:939–42. https://doi.org/10.1002/lsm.21141.
49. Ramien ML, et al. Quality of life in pediatric patients before and after cosmetic camouflage of visible skin conditions. J Am Acad Dermatol. 2014;71:935–40. https://doi.org/10.1016/j.jaad.2014.07.029.