KLIPPEL–TRANAUNAY, PARKES WEBER AND STURGE–WEBER SYNDROMES (INCLUDING KASABACH–MERRIT PHENOMENA)

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Introduction

The following chapters consider Klippel–Tranaunay syndrome (OMIM # 149000), Parkes Weber syndrome and Sturge–Weber syndrome (OMIM # 185300) together because all three have various types of vascular malformations and overgrowth involving the limbs in Klippel–Tranaunay and Parkes Weber syndromes and the head (but also other body regions) in Sturge–Weber syndrome (Cohen 2006, Cohen et al. 2002). Besides Sturge–Weber syndrome the other two conditions (or three if one includes Kasabach–Merrit syndrome) are not truly neurocutaneous disorders because their nervous system involvement is of limited extent if any and extremely infrequent. In these chapters however we have treated them all in consideration of their relevance for differential diagnosis.

These disorders have been also said to overlap with each other (Happle 1993, 2003; Vissers et al. 2003, reviewed in Gorlin et al. 2001), but they should be considered separate clinical entities that for the most part occur sporadically and have different clinical manifestations and types of complications (Cohen 2000, 2002, 2006; Cohen et al. 2002). In this connection, some authors (Cohen 2002, 2006; Cohen et al. 2002; Gorlin et al. 2001; Hand and Frieden 2002) find it essential to discuss along with the three main syndromes vascular tumours vs. vascular malformations and also the Kasabach–Merrit phenomenon.

Current terminology

Klippel–Tranaunay syndrome consists of a complex constellation of anomalies that includes (a) combined vascular malformations of the capillary, venous, and lymphatic types, (b) varicosities of unusual distribution, in particular a lateral venous anomaly observed during infancy or childhood, and (c) limb enlargement (Berry et al. 1998; Cohen 2000, 2002, 2006; Cohen et al. 2002; Gorlin et al. 2001).

The main clinical features of *Parkes Weber syndrome* are enlarged arteries and veins, capillary or venous malformations, and enlargement of a limb (Cohen 2002, 2006; Cohen et al. 2002; Gorlin et al. 2001).

Sturge–Weber syndrome also known as encephalofacial or encephalotrigeminal angiomatosis or meningofacial angiomatosis is characterised by a capillary malformation involving the brain and meninges with or without choroid (and/or episclera or conjunctive) and skin (facial V1–V3 territory including the mouth, pharynx and nasal mucosa or often the rest of the body) involvement (Baselga 2004, Cohen 2006, Gorlin et al. 2001, Thomas-Sohl et al. 2004).

Kasabach–Merrit syndrome is better designated "*Kasabach–Merrit phenomenon*" because it is likely to be pathogenetically variable (as one of its features, thrombocytopenia occurs in various types of vascular neoplasms) and has variable therapeutic response. The term is frequently applied (incorrectly) to

patients with extensive venous or lymphatic venous malformations who develop a localised intravascular coagulopathy (chronic consumptive coagulopathy) in which the platelet count is minimally depressed (varying from 50,000 to 150,000/mm^3). In contrast, thrombocytopenia is profound varying from 3,000 to 60,000/mm^3 with an average of <25,000/mm^3 (Cohen 2006, Sarker et al. 1997). This distinction has important treatment implications as for example, heparinisation might be indicated in consumptive coagulopathy in vascular malformations, particularly with thrombotic complications, but is contraindicated in Kasabach–Merrit thrombocytopenia found with vascular tumours (Sarkar et al. 1997; Cohen 2002, 2006). Similar diagnostic implications are applied to Kasabach–Merrit phenomenon vs. Klippel–Tranaunay syndrome (see below) (Cohen 2002, 2006; Cohen et al. 2002; Gorlin et al. 2001).

Nosologic considerations on vascular confusion

The terminology describing congenital vascular birthmarks has been a source of confusion in the medical literature. Discrepant terms still exist (Hand and Frieden 2002, Vissers et al. 2003) and physicians have used multiple names to characterise the same anomaly. This persistent ambiguity has generated a increasing taxonomy (Cohen 2002, 2006; Happle 1993, 2003). Resolving vascular confusion has been a primary mission of John Mulliken and his co-workers (Burns et al. 1991; Cheung et al. 1997; Enjorlas and Mulliken 2000; Enjolras et al. 2001; Grevelink and Mulliken 1999; Martinez-Perez et al. 1995; Mulliken 1993, 1997, 1998; Mulliken and Burrows 2001; Mulliken and Glowacki 1982; Mulliken and Young 1988; Mulliken et al. 2006; Sarkar et al. 1997; Takahashi et al. 1994; Vikkula et al. 1998, 2001; reviewed in Hand and Frieden 2002; Cohen 2002, 2006; and Mulliken et al. 2006).

Mulliken and Glowacki (1982), Mulliken and Young (1988)and Mulliken et al. (2006) published a biological classification system which has become the most widely accepted (Cohen 2002, 2006; Hand and Frieden 2002) framework for classifying vascular birthmarks and is accepted as the official classification schema by the International Society for the Study of Vascular Anomalies (ISSVA) (Enjolras and Mulliken 2000, Mulliken et al. 2006). In the Mulliken classification (Mulliken 1993, Mulliken and Glowacki 1982, Mulliken et al. 2006) a distinction is made between vascular tumours and vascular malformations based on cellular kinetics and clinical behaviour. *Vascular tumours* have endothelial hyperplasia with rapid postnatal growth followed by slow involution. In contrast, *vascular malformations* are characterised by flat endothelium, and growth of the lesion is commensurate with growth of the child. An additional category, introduced by Burns et al. (1991) are *macular stains* (commonly knows as nevus flammeus) which are flat, pink, and irregularly outlined vascular lesions that are transient and disappear (Cohen 2006). The ISSVA classes for *tumours* include: (a) haemangioma of infancy (PHACE syndrome, diffuse neonatal haemangiomas and lumbosacral haemangiomas); (b) Kaposiformi haemangioendothelioma (with or without Kasabach–Merrit phenomenon); (c) Tufted angioma (with or without Kasabach–Merrit phenomenon); and (d) other vascular tumours. Vascular *malformations* of the skin can be assigned to one of five groups based on histological and clinical appearance: (a) *simple malformations (pure types)* [*fast flow*: arterial (AM) or arteriovenous (AVM) including also arteriovenous fistulas (AVF); *slow flow*: capillary (CM) including Cobb syndrome, Sturge–Weber syndrome, Cutis marmorata telangiectatica congenital, Phakomatosis pigmentovascularis, Robert-SC Phocomelia, Wiedemann-Beckwith syndrome and Hereditary neurocutaneous angioma; lymphatic (LM); and venous (VM) including Blue-rubber Bleb Nevus syndrome and glomangiomas]; or (b) *combined lesions (complex types)* which can be localised or syndromic [CLM including Klippel–Tranaunay syndrome and Proteus syndrome; CVM including Hyperkeratotic cutaneous capillary-venous malformations; CLVM including Parkes Weber syndrome and LVM] (Cohen 2002, 2006; Mulliken and Glowacki 1982; Mulliken 1993; Mulliken et al. 2006). All the above conditions are extensively treated in the present and other chapters and therefore we

refer the reader to these sections. It must be noted however that these malformations can be isolated or be accompanied by soft tissue or bone hyper- or hypotrophy and other soft tissue abnormalities or tumours and extra-vascular malformations (Cohen 2001, Mulliken 1988). It is sometimes the combination of these associated features which better characterises a syndromic spectrum.

By using this classification system physicians are able to classify 90% of vascular anomalies seen in infants, which can be distinguished from one another by history taking and physical examination, without the need for ancillary studies such as ultrasonographic studies, computerised tomography (CT), magnetic resonance imaging (MRI) or histological examination (Hand and Friedman 2002, Vissers et al. 2003). In this respect however Hand and Frieden (2002) and Happle (1993, 2000, 2003) have been also careful to point out that in rare instances, vascular lesions may not behave in accordance with the modern classification of vascular anomalies (Cohen 2002, 2006). There are examples of clinical and histological overlaps between vascular tumours and malformations (Garzon et al. 2000) or rare congenital haemangiomas that do not involute (Enjolras et al. 2001) or histologically diagnosed haemangiomas of adulthood that do not regress (Mulliken and Burrows 2001). In addition, diagnostic difficulties exist when vascular anomalies present after infancy or the features which should distinguish tumours from malformations may not be evident on a single exam. In these cases laboratory tests (North et al. 2000) or imaging (Cohen 2002, 2006) may help. MRI is the most informative modality for studying odd vascular malformations and can demonstrate flow characteristics and the extent of involvement within tissue planes. In addition, an MRI with gadolinium administration can distinguish lymphatic from venous malformations, MR venograms or phlebography/venography can document accessory (deep) venous anomalies in the limbs. CT and/or MRI can also demonstrate arteriovenous malformations, intraosseous vascular malformations or leptomeningeal abnormalities (Cohen 2002, Konez et al. 2003).

Several case reports published in the last 20 years, claimed that often there is no clear distinction between some disorders with clinical and biological overlaps (Happle 2003, Vissers et al. 2003) and umbrella terms (such as for example Sturge–Weber–Klippel–Tranaunay syndrome) have been proposed to encompass mixing and coexisting phenotypes. Patients with Sturge–Weber syndrome have been described with other vascular abnormalities including the spectrum of Klippel–Tranaunay syndrome or associated pigmentary anomalies such as the blue nevus of phakomatosis pigmentovascularis (Al Robaee et al. 2004, Cho et al. 2001, Diociaiuti et al. 2005, Hagiwara et al. 1998, Lee et al. 2005, Saricaoglu et al. 2002, Uysal et al. 2000). The coexistence of clinical and/or imaging features of Sturge–Weber syndrome, Klippel–Trenaunay syndrome and phacomatosis pigmentovascularis in the same patient is not an exceptional event. In this respect and in agreement with other authors (Cohen 2000, 2002, 2006; Cohen et al. 2002; Gorlin et al. 2001) we believe that this conventional thinking can be seriously challenged. As it occurred with the different forms of neurofibromatosis (Ruggieri 1999, 2000, 2001; Ruggieri and Huson 1999, 2001) after careful literature review none of these mixed phenotypes stood up as a separate disorder (with the exception of true newly recognised disorders which however present with their own unique features). However, it could be that the loci of the responsible genes for all (or some of) these conditions (e.g., Sturge–Weber, Klippel–Trenaunay and Parkes Weber syndromes) might be probably close neighbours (see below and Tian et al. 2004) on that the protein products of the defective gene(s) share common pathways or cooperate with each other.

Here below we analyse this important topic with regard to Klippel–Trenaunay, Parkes Weber and Sturge–Weber syndromes tabulating the criteria for distinction between the three disorders.

Klippel–Tranaunay vs. Parkes Weber vs. Sturge–Weber: overlaps or variations on a theme?

The multiple, combined vascular malformations and skeletal asymmetry characteristics of Klippel–

Tranaunay syndrome and Parkes Weber syndrome and the capillary malformation (nevus flammeus) typical of Sturge–Weber syndrome often occur in the same patients, establishing them as overlapping disorders (Happle 1993, 2000, 2003; Vissers et al. 2003; Wilson 2004).

Conventional wisdom about *Klippel–Tranaunay syndrome* and *Sturge–Weber syndrome* include reviewed in (Cohen 2002, 2006): 1) overlap between Klippel–Tranaunay and Sturge–Weber syndromes; 2) addition of arteriovenous fistulas and renaming of the disorder as Klippel–Tranaunay-Weber syndrome; 3) the presence of a bleeding diathesis of the Kasabach–Merrit type in Klippel–Tranaunay syndrome; and 4) familial aggregation in either syndrome with various genetic interpretations (Cohen et al. 2002, Gorlin et al. 2001). *Sturge–Weber syndrome* is defined as a capillary malformation of the leptomeninges with or without choroid and facial V1 or V1–V3 involvement (Cohen 1998). Capillary malformations of the skin may extend to appear anywhere on the body, including the upper and lower limbs. Presumed cases of "*merged*" *Klippel–Tranaunay syndrome* and *Sturge–Weber syndrome* most always represent Sturge–Weber syndrome with capillary malformations only below the head and neck. Few of these cases however could represent "combined cases" because of the presence of essential manifestations of Klippel–Tranaunay syndrome such as lymphatic malformations, lateral venous anomaly, lymphatic vesicles, and venous flares within the capillary malformation, limb enlargement, and macrodactyly (Cohen 2006). On the other hand, most large surgical series of Klippel–Tranaunay syndrome patients do not include patients with capillary malformations involving the face (Lindenauer 1965, Mulliken 1999, Serville 1985, Young 1998). Hemiparesis, present in some cases of Sturge–Weber syndrome, may result in a hypotrophic limb. Overgrowth may occur in Sturge–Weber syndrome but tends to be minor and is always secondary to the vascular anomaly. Hypertrophy of the area with the capillary malformation in the face may occur with time and overgrowth of the bony maxillae is common in Sturge–Weber syndrome. When the capillary malformation involves the ear, its length may be greater than that of the contralateral ear. Rarely, a digit may be enlarged. In contrast, overgrowth in Klippel–Tranaunay syndrome is striking and macrodactyly may occur in the "uninvolved" limb (reviewed in Cohen 2002, 2006).

Parkes Weber and *Klippel–Tranaunay syndromes* are similar but some important distinctive features exist: 1) slow-flow venous malformations are predominant in Klippel–Tranaunay syndrome (vs. fast-flow vascular malformations in Parkes Weber syndrome), but arteriovenous (AV) fistulas are always found in Parkes-Weber syndrome; 2) the colour of the cutaneous malformation in Parkes-Weber syndrome is

Table 1. Criteria for distinction between Klippel–Tranaunay, Parkes Weber and Sturge–Weber syndromes

Klippel–Tranaunay	Slow-flow, combined vascular (capillary, lymphatic and venous) involving limb(s) and/pr trunk. Bluish to purplish colour of vascular malformation. Insignificant arteriovenous fistula. Very common lateral venous anomaly. Lymphatic vesicles and venous flares found. Disproportionate limb enlargement involving soft tissue and bone; macrodactyly (particularly of toes). Good prognosis (occasional pulmonary embolia).
Parkes Weber	Fast follow, combined vascular (capillary, arterial, and venous) involving upper/lower limbs; usually pink and more diffuse colour of vascular malformation. Significant arteriovenous fistula. Lateral venous anomaly, lymphatic vesicles and venous flares not found. Arm or leg length discrepancy. More problematic prognosis (bradycardia, cardiac enlargement with limb amputation).
Sturge–Weber	Capillary malformation of leptomeninges with or without choroid (episclera/conjunctive) and facial (V1–V3) involvement. Capillary malformations can occur elsewhere in the body. Glaucoma. Common associated neurological manifestations including seizures, neurological deficits, stroke-like episodes, headache, developmental delay, lower limb(s) hemihyperplasia.

Adapted from Cohen 2002, 2006 and Cohen et al. 2002.

usually more diffuse and pinker than that observed in Klippel–Tranaunay syndrome; 3) lymphatic malformations do not occur and no lymphatic vessels are found in the discoloured skin of Parkes Weber syndrome; and 4) the prognosis in Parkes Weber syndrome is more problematic particularly in those developing bradycardia leading to cardiac failure, cardiac enlargement and cutaneous ischemia requiring limb amputation. We summarise the main differences in Table 1.

By applying these simple diagnostic criteria (e.g., capillary malformation of leptomeninges and/or choroid and/or facial trigeminal regions vs. combined vascular lesions) overlaps and mixed phenotypes become almost always untenable. For instance in a recent case reported by Vissers et al. (2003) Sturge–Weber syndrome was claimed to coexist with Klippel–Tranaunay syndrome. However, careful and critical review of clinical summary and accompanying illustrations shows this was a Sturge–Weber syndrome because of "widespread capillary malformation on the face", neuroimaging demonstration of "leptomeningeal dysplasia at the level of the right occipital lobe with ipsilateral enlarged choroid plexus and subsequent "cortical atrophy in the same anatomical region" associated to "glaucoma of the right eye occurred at the age of 11 years", "complex partial seizures" and "psychomotor retardation". Additional areas of vascular (capillary) malformation in a mosaic pattern over the buttock and left leg and soft tissue overgrowth (and bone hyperplasia) in the areas within the vascular anomaly in the leg. Assignment of this patient to two different clinical entities (Vissers et al. 2003) or designation of new terms (such as Sturge–Weber–Klippel–Tranaunay syndrome) (Happle 2003) may be unjustified on clinical and imaging grounds.

One important issue in favour of possible overlaps between Klippel–Tranaunay, Parkes Weber and/or Sturge–Weber syndromes or a continuum spectrum of disorders is the recently proposed *angiogenic/vasculogenic model* which has been applied to Klippel–Tranaunay syndrome (Klessinger and Christ 1996) (see also chapter on Klippel–Tranaunay syndrome). This model suggests that the distinctive midline demarcation in Klippel–Tranaunay syndrome may be due to defined boundaries for endothelial migration (bounded by the notocord) which cause defects in axial blood vessel formation (Sumoy et al. 1997). The genetic alteration that results in Klippel–Tranaunay syndrome may be located in endothelial cells altered in the process of vessels formation and the cellular lesion leading to the manifestations of Klippel–Tranaunay syndrome may be related to persistence of foetal structures (i.e., the foetal dermal capillary web an foetal vasculature) (Baskerville et al. 1985). The morphogenetic defect causing Klippel–Tranaunay syndrome thus may affect the normal process of remodelling of developing vascular structures as *vasculogenesis* (the process of generation of primitive vasculature networks which involves the differentiation of endothelial cells from mesenchimal progenitors to form a primary vascular plexus or network) and *angiogenesis* (the process that occurs once the primary plexus is established and new capillaries are formed by sprouting/budding and non sprouting/intussusception, or splitting) occur, perhaps by an interference with apoptosis required for vessel remodelling during embryogenesis. A series of ligands appear to be critical regulators of angiogenesis and vasculogenesis including members of the vascular endothelial growth factor (VEGF) (Cohen 2006, Klagsbrun and D'Amore 1996). Recently, an elegant combination of human genetics and functional analysis allowed the discovery of the first *susceptibility gene* for Klippel–Tranaunay syndrome (Tian et al. 2004, Whelan et al. 1995): the VG5Q (angiogenic factor VG5Q) gene (on chromosome 5q13.3) expressed strongly in blood vessels and secreted upon initiation of angiogenesis. Over expression of VG5Q stimulates angiogenesis and suppression of VG5Q by RNA or anti sense inhibits vessel formation. On the basis of the model of Tian et al. (2004) and according to the hypothesis of paradominance of Happle (1993, 2000, 2003) patients with the VG5Q E113K mutation may carry a second mutational hit in VG5Q or another gene within the affected tissue (Tian et al. 2004).

Thus, it could be that susceptibility genes may cause localised phenotypes characterised by either simple [Sturge–Weber syndrome with lesions confined to one or more tissues (i.e., skin, eye and leptomeninges) in the head only] or mixed

(Klippel–Tranaunay or Parkes Weber syndromes) vascular malformations or more generalised phenotypes (Sturge–Weber syndrome with head and trunk involvement) or ultimately to "merged" (overlapping) types of vascular malformations such as phakomatosis vasculovascularis or mixed epidermal/vascular malformations such as phakomatosis pigmentovascularis.

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