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# Review Sudden death and the forensic evaluation of neurocutaneous syndromes

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#### ABSTRACT

On occasion the forensic evaluation of individuals who have died suddenly and unexpectedly may reveal intracranial vascular abnormalities such as capillary, venous- and arteriovenous malformations. Such vascular abnormalities may form part of a heterogeneous group of disorders called neurocutaneous syndromes and involve the skin, nervous system and other organ systems. These unusual conditions include Sturge–Weber, Osler–Weber–Rendu, Klippel–Trenaunay, Von Hippel-Lindau, Proteus and Wyburn-Mason syndromes in addition to ataxia telangiectasia. Causes and mechanisms of unexpected death include epileptic seizures, intracranial haemorrhage and thromboses. Differentiating these conditions at autopsy is important because of variable inheritance patterns and occasionally inaccurate clinical classifications. The autopsy evaluation requires review of the medical and family histories, and full external and internal examinations with photographic documentation and histologic sampling of lesions. Formal neuropathology, storage of blood and tissues for molecular studies if required, and liaison with a medical geneticist should be considered.

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## 1. Introduction

The neurocutaneous syndromes, or phakomatoses, are a very heterogenous group of congenital disorders of neuroectodermal origin with lesions involving the skin, nervous and other organ system. Although more than 40 conditions have been included under this umbrella there is no consensus on the final classification.<sup>1,2</sup> For example, while neurofibromatosis, tuberous sclerosis, Von Hippel-Lindau disease and Sturge–Weber syndrome are usually included, Osler–Weber–Rendu, Klippel–Trenaunay and proteus syndromes may not always be found in reviews.<sup>2,3</sup>

Sudden death, although uncommon, may be associated with epilepsy or haemorrhage at any age, and neurocutaneous disorders have been found to be a risk factor in 3.9% of cases of childhood stroke.<sup>4</sup>

Review of coronial files in South Australia revealed four cases of neurocutaneous syndromes where the underlying syndrome was directly involved in the mechanism of death. The details of one case have been previously published<sup>5</sup> and the features of the remaining three cases are now reported to demonstrate features of these conditions and diagnostic issues and difficulties that may arise.

# 2. Case 1

A 27-year-old woman with known Sturge–Weber syndrome and a long history of epilepsy and non-compliance with medications arrested during an episode of status epilepticus. She was initially successfully resuscitated but gradually deteriorated over the next few hours and died. Her past history included onset of seizures at around 18 months of age with the subsequent development of left sided facial hypertrophy.

At autopsy a large haemangioma involving the left side of the face was noted together with grossly oedematous and congested lungs and bilateral pleural effusions. Toxicology revealed subtherapeutic levels of phenytoin and carbamazepine, but was otherwise negative.

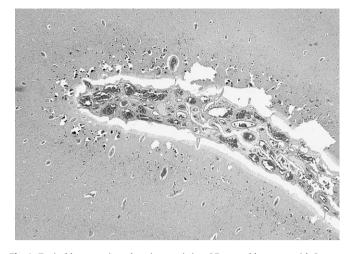
Neuropathology showed left temporo-occipital leptomeningeal angiomatosis (Fig. 1) involving the left middle and inferior temporal gyri and the inferolateral aspect of the left occipital lobe over a total area of  $10.5 \times 4.5$  cm. The underlying cortex was atrophic, in areas measuring approximately 1 mm, with focal calcification. Death was attributed to hypoxic ischaemic encephalopathy complicating status epilepticus.

# 3. Case 2

A 67-year-old woman was found dead at her home address lying on her back. At the age of 59 years she had consulted a

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**Fig. 1.** Typical leptomeningeal angiomatosis in a 27-year-old woman with Sturge–Weber syndrome who died of hypoxic brain damage following an episode of status epilepticus (case 1). Adjacent cortical calcification is present (Haematoxylin & Eosin, H&E,  $\times$ 40).

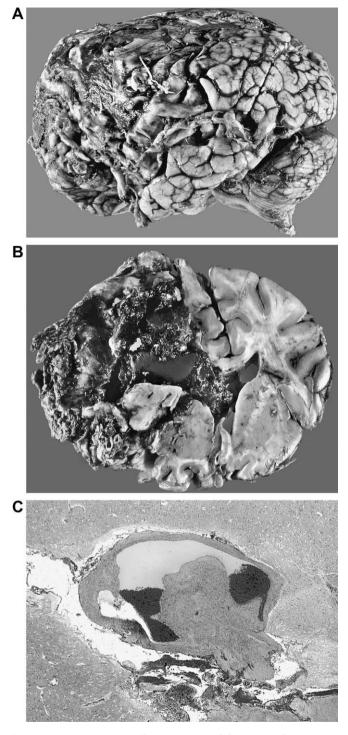
neurologist due to progressive memory failure and deterioration of cognitive functions. She had a past medical history of frequent nose bleeds and migraine since the age of 12 years. Her mother had died of an unknown pulmonary problem when the deceased was a child. Neurological investigations revealed striking telangiectatic vessels over the face, lips, tongue and hand, with bilateral carotid and orbital bruits. Osler-Weber-Rendu syndrome was suspected and was confirmed by MRI scan and cerebral angiography which demonstrated an extensive arteriovenous malformation in the left cerebral hemisphere with numerous dilated vessels extending from the frontal lobe through to the posterior parietal and occipital lobes, and from the middle cranial fossa into the basal ganglia and the vertex. There was significant mass effect with effacement of the left lateral ventricle and shift of the midline toward the right. CT scan of the lungs showed two small pulmonary arteriovenous malformations located in the right middle and lower lobes. Radiotherapy for the cerebral lesions was offered but was declined. Two years after diagnosis she was admitted to hospital with migraine and associated weakness with parasthesia of the right hand and expressive dysphasia, however a CT scan showed no signs of haemorrhage, infarct or change in size of the lesions.

At autopsy numerous ectatic vessel were identified in the skin, lungs, spleen, thyroid gland and throughout the gastrointestinal tract. Neuropathological examination revealed a large left frontal lobe haemorrhage extending to the cortical surface and into the ventricular system. A complex network of ectatic vessels was located within the left frontal pole adjacent to the area of haemorrhage extending from the leptomeninges into the underlying cerebral parenchyma (Fig. 2).

# 4. Case 3

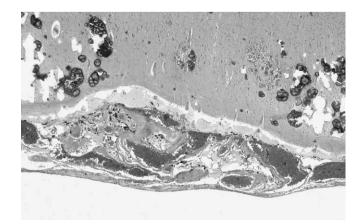
A 28-year-old man was found dead in bed. He had suffered from epilepsy, hearing loss, right homonymous hemianopia, haemangiomas and mental impairment and a clinical diagnosis of Klippel– Trenaunay–Weber syndrome had been made. The deceased had previously undergone laser debulking of haemangiomas of the lip.

At autopsy multiple cutaneous capillary malformations (portwine stains) were noted on the face bilaterally (most prominently on the left side with clear midline demarcation), on the left side of the chest (again with a clear midline demarcation), on the left arm and on both legs. There were no varices of the legs.



**Fig. 2.** A large arteriovenous malformation in the left frontal lobe of a 67-year-old woman with Osler–Weber–Rendu syndrome (case 2) (A) that was associated with extensive lethal intracerebral haemorrhage (viewed posteriorly on coronal sectioning of the brain (B). A typical ectatic vessel forming part of the arteriovenous malformation (C) (H&E  $\times$ 20).

Neuropathologic evaluation revealed left cerebral hemispheric atrophy affecting particularly the left occipital lobe with left occipital parenchymal calcification, left hippocampal atrophy and leptomeningeal angiomatosis (Fig. 3) with diffuse melanosis. Toxicology revealed a therapeutic level of the anticonvulsant vigabatrin in the blood. Death was attributed to epilepsy associated with vascular abnormalities in the brain.



**Fig. 3.** Clusters of abnormal hyalinized vessels in a 28-year-old man with likely Sturge–Weber syndrome (case 3). Prominent adjacent cortical calcification is again present (H&E, x 20).

#### 5. Discussion

The assessment and classification of the neurocutaneous syndromes is complicated by variation in the terminology used for the underlying vascular lesions. Vascular abnormalities can be classified as haemangiomas, vascular malformations and macular 'stains', or so-called nevus flammeus.<sup>6-8</sup> Haemangiomas differ from vascular malformations as they are often not present at birth and show rapid growth with slow involution, while malformations are present at birth (although are not necessarily evident), normally only grow proportionately with the rest of the tissues, and do not disappear spontaneously.9 Haemangiomas are also only rarely associated with other dysmorphic features, such as in PHAC-ES syndrome (malformations of the posterior fossa, facial haemangiomas, arterial cerebrovasular, cardiovascular and eye anomalies, with sternal clefting/supraumbilical raphe), while true malformations are often found in patients with other dysmorphic features.<sup>6,10</sup> Haemangiomas have a female predominance (M:F = 3:1), while vascular malformations are equally distributed between males and females.<sup>9</sup> Haemangiomas have been termed capillary haemangiomas, capillary-cavernous haemangiomas, strawberry marks and benign haemangioendotheliomas. Vascular malformations may involve arterial vessels with high blood flow, or may be limited to capillary, lymphatic or venous channels with slower flow; combined lesions may also occur. These features are summarised in Table 1.

Microscopically, haemangiomas are characterized by plump endothelial lining cells, increased cell turnover, increased numbers

#### Table 1

Classification of vascular malformations (adapted from Mulliken 1993 and Cohen  $2006)^{7,12}$ .

Vascular malformations	
Single channel Arterial	Fast flow
Aneurysm, coarctation, ectasia Arteriovenous fistula	
Arteriovenous malformation	
Capillary Lymphatic Venous	Slow flow
Complex/combined Capillary–lymphatic	Slow flow
Capillary–venous Capillary–lymphatic–venous Lymphatic–venous	

of mast cells, and multilaminated basement membranes. This contrasts with vascular malformations that have flatter endothelial cells, with slower cellular turnover and normal mast cell counts and basement membranes<sup>8,9,11</sup> (Table 2). A wide variety of manifestations and conditions are associated with these vascular lesions, as detailed below.

#### 5.1. Sturge-Weber syndrome

Sturge–Weber syndrome, or encephalotrigeminal angiomatosis, is a syndrome characterised by (1) capillary facial nevi (naevus flammeus) mostly unilateral with a port-wine appearance, primarily located in the  $V_1$  or  $V_1 - V_2$  region of the trigeminal nerve, (2) meningeal angiomas in the pia mater, (3) congenital glaucoma and (4) lesions in the choroid plexus where the normal choroid tufts are replaced by thin-walled capillaries, small veins and angiomatous cavernomas resulting in enlargement of the choroid plexus and calcifications.<sup>12–15</sup> Port wine stains may also be present on the trunk and extremities, and homonymous hemianopia and mental handicap are also frequent findings.<sup>12,15</sup>

The disorder is sporadic, but familial cases occur, with a prevalence of around 1 per 50,000 live births.<sup>13</sup> Epilepsy occurs in approximately 75–90% of affected patients, with the presence of bilateral facial port-wine stains increasing the risk.<sup>13,15</sup> Seizures are often resistant to medication, especially in cases of early onset disease, and haemorrhagic and ischaemic stroke may occur.<sup>4,16</sup> Death, as in case 1, may result from the complications of epilepsy.

#### 5.2. Osler-Weber-Rendu syndrome

Osler-Weber-Rendu or hereditary haemorrhagic telangiectasia is an autosomal dominant disorder with high penetrance and extremely variable expressivity.<sup>17</sup> The prevalence of the disorder is estimated to be around 2.5-19.4 per 100,000 of the population.<sup>18,19</sup> Genetic studies have revealed that most cases of hereditary haemorrhagic telangiectasia result from mutations in the endoglin gene on chromosome 9 (HHT type 1) or the activin receptor like kinase 1 gene on chromosome 12 (HHT type 2), with reduced incidence of pulmonary involvement in the latter.<sup>19-22</sup> According to the Curaçao Criteria formulated in 2000, a definitive diagnosis can be made when three out of the following four criteria are present: (1) spontaneous and recurrent epistaxes, (2) telangiectases - multiple at characteristic sites, (3) visceral lesions such as gastrointestinal telangiectasia and arteriovenous malformations in the brain, lungs, liver and spinal cord and (4) a family history with an affected first degree relative.<sup>23</sup> Cerebral arteriovenous malformations are found in around 12-15% of patients with this disorder and appear to be slightly more common in females.<sup>24,25</sup> Vascular malformations of the spinal cord have been described but are very rare.<sup>26</sup>

Cerebral arteriovenous malformations typically manifest with migraines, seizures, syncope, transient or permanent focal motor deficits or visual disturbances, progressive neurological deficits

## Table 2

Differential features of haemangiomas and vascular malformations (adapted from Mulliken 1982, Glowacki 1982, Finn 1983)<sup>8,9,11</sup>.

Haemangiomas	Malformations
1:2.4–5 male:female ratio	1:1 male:female ratio
Often not present at birth	Present at birth
Rapid growth and slow involution	Grow proportionally with other
	tissues
Endothelial hyperplasia	Flat endothelium
Multilaminated basement membrane	Normal basement membrane
Increased number of mast cells during proliferative phase	Normal mast cell count

(as in case 2), or subarachnoid haemorrhage, although almost half of cases are asymptomatic.<sup>5,25,26</sup> Neurological symptoms may also result from portal-systemic encephalopathy, or secondary to complications of pulmonary lesions such as right-to-left shunting of blood with hypoxemia, air embolism or brain abscesses.<sup>26</sup> Sudden death may occur secondary to epilepsy, brain abscesses or intracranial haemorrhage, as in case 2, or from lung or gastrointestinal tract haemorrhage.<sup>5</sup>

#### 5.3. Klippel–Trenaunay syndrome

Confusion exists concerning the exact manifestations of Klippel–Trenaunay syndrome as arteriovenous fistulas are sometimes included in the diagnostic criteria thus merging it with Parkes Weber syndrome. Because of overlapping symptoms and findings it is also often confused with Sturge–Weber syndrome.<sup>12,27</sup> Accepted criteria for Klippel–Trenaunay syndrome include (1) combined vascular malformations of capillary, venous and lymphatic types, (2) varicose veins observed during infancy or childhood and (3) limb enlargement of one or more limbs, often with macrodactyly (particularly of the toes). However, over one third of affected individuals will not have all three of these findings.<sup>27,28</sup> As there should be no significant arteriovenous fistulas or capillary malformations involving the face or craniofacial region<sup>27,29</sup> it appears likely that case 3 was clinically misclassified and was Sturge–Weber syndrome.

The lower limbs are involved in 95% of cases with only 5% involvement of the upper limbs.<sup>27</sup> Intracranial findings include aneurysms and enlargement of the choroid plexus in association with subcortical calcification. Occasionally spontaneous intracranial haemorrhage may occur in the apparent absence of arteriovenous malformations or aneurysms. Some authors argue that such cases (often described as Klippel–Trenaunay with Sturge–Weber, or Klippel–Trenaunay–Weber syndrome) are, in fact, misdiagnosed cases of Sturge–Weber syndrome with limb involvement<sup>4,12,14,30–32</sup>, as is likely in case 3.

Klippel–Trenaunay syndrome is sporadic and the etiology remains obscure although it has been suggested that it may be caused by mesodermal defect during development leading to persistence of microscopic arteriovenous communications in developing limb buds.<sup>29</sup> Generally patients with Klippel–Trenaunay syndrome have a good prognosis, although there is an increased risk of pulmonary emboli and other consequences of hypercoagulability due to the vascular malformations.<sup>12,33</sup> Fatal pulmonary embolism arising from peripheral vascular malformations may occur at any age, including early childhood.<sup>34</sup>

Although it is often stated that Kasabach–Merritt phenomenon may complicate Klippel–Trenaunay syndrome, this is not the case if strict diagnostic criteria are applied.<sup>27</sup> While vascular abnormalities such as venous or lymphaticovenous malformations may cause intravascular coagulopathy, only kaposiform haemangioendotheliomas and tufted angiomas develop thrombocytopenia of such a degree to meet the criteria for Kasabach–Merritt phenomenon. The term is, however, often used more broadly to describe a wide range of vascular malformations with complicating thrombocytopenia.<sup>27,35</sup>

#### 5.4. Ataxia telangiectasia

Ataxia telangiectasia, also known as Louis-Bar syndrome, is a rare autosomal recessive multisystem disorder with progressive motor impairment, oculocutaneous telangiectases, recurrent sinopulmonary infections, progressive immunodeficiency, enhanced sensitivity to ionizing radioactivity and a high risk of lymphoreticular malignancies.<sup>3,36,37</sup> Diagnostic criteria include (1) an ataxic gait in the first three years of life (2) oculomotor signs and dysarthria by early school years (3) worsening limb ataxia, swallowing problems, and peripheral neuropathy, together with at least one of the following: (4) ocular telangiectasia (5) elevated serum  $\alpha$ -fetoprotein level after one year of age or (6) spontaneous or radiation-induced chromosomal breakage.<sup>37</sup>

Patients with ataxia telangiectasia have a significantly reduced life expectancy, with a median survival of around 25 years, with deaths due to malignancy, pneumonia, or secondary to multiple central nervous system telangiectatic vascular abnormalities that can result in intracranial haemorrhage. Even carriers of the disease are known to have an increased mortality primarily due to malignancy and ischaemic heart disease.<sup>38–41</sup>

### 5.5. Von Hippel-Lindau syndrome

Von Hippel-Lindau syndrome is an autosomal dominant syndrome resulting from a deletion or mutation in the tumor suppressor gene on chromosome 3p25.<sup>42</sup> The disorder is characterised by vascular tumors (most commonly benign haemangioblastomas) localised in the cerebellum, brain stem, spinal cord and retina, although tumors have been described throughout the central nervous system.<sup>42,43</sup> Affected individuals have an increased risk of developing other benign and malignant tumors such as visceral haemangioblastomas, cysts of the kidney, liver, epididymis, and pancreas, endolymphatic sac tumors (causing deafness), pheochromocytomas (only with certain mutations), and renal cell carcinomas (in up to 70% of cases).<sup>43,44</sup>

Traditionally the diagnosis can be made when a cerebellar haemangioblastoma is found in conjunction with either a retinal haemangioblastoma, or pancreatic cysts, or renal or epididymal abnormalities. If there is a family history, only one of these findings needs to be present to establish the diagnosis.<sup>44,45</sup>

The estimated median survival is 49 years, with renal cell carcinomas accounting for most deaths.<sup>43</sup> Epilepsy is not a common finding in Von Hippel-Lindau syndrome as the majority of haemangioblastomas are small in size (ranging from 8 to11 mm). The risk of haemorrhage is also low, occurring in only 0.0024 persons per year, with tumor size as the most important risk factor.<sup>46,47</sup>

### 5.6. Proteus syndrome

Proteus syndrome is an extremely rare hamartoneoplastic disorder with only approximately 200 cases described in the literature, one of them being John Merrick the so-called "elephant man".<sup>48–50</sup> The disease is characterised by a (1) disproportionate overgrowth, (2) connective tissue or epidermal nevi, (3) vascular malformations, (4) lipomas, (5) regional absence of fat, and (6) facial abnormalities. Sporadic occurrence, a progressive course and a mosaic distribution of lesions are now required diagnostic features.<sup>51</sup> It is suspected that the non-mosaic variant of the disease is lethal *in utero*.<sup>49</sup>

The etiology of proteus syndrome is unknown, however because of the presence of vascular malformations individuals who are affected have an increased risk of dying from pulmonary embolism, in addition to an increased risk of sudden death from epilepsy (although intracranial vascular malformations are rare).<sup>48,52,53</sup>

#### 5.7. Wyburn-Mason syndrome

Wyburn-Mason syndrome, or brain-retino-facial angiomatosis, is an extremely rare syndrome with less than 30 cases reported over the past 34 years.<sup>54</sup> It is a congenital disease with (1) ipsilateral arteriovenous malformations of the midbrain, (2) vascular abnormalities of the visual pathways together with (3) facial nevi in most cases. The diagnosis can be made even with only one or two of the characteristic features present.<sup>54,55</sup> Although many of

Table 3

An autopsy approach to the neurocutaneous syndromes.

1	Review of complete medical and family history prior to autopsy if possible
2	Full external examination with:
	i. Color photographs of all lesions
	ii. Histologic sampling of cutaneous lesions
3	Full internal examination with:
	i. Color photographs of all lesions
	ii. Histologic sampling of lesions
4	Formal neuropathologic examination where possible
5	Liaison with medical geneticist
6	Blood and tissues kept for molecular studies if required
_	

the arteriovenous malformations remain asymptomatic, rupture with intracerebral or subarachnoid haemorrhage is a theoretical possibility. Deaths due to stroke or epilepsy do not appear to have been an issue with this disorder.54

## 5.8. Parkes weber syndrome

The Parkes Weber syndrome was first reported in 1907 by. Frederick Parkes Weber<sup>12</sup> but is not usually considered to be part of the spectrum of neurocutaneous disorders. However as it is sometimes included under the umbrella of Klippel-Trenaunay syndrome, and shares many characteristics with Sturge-Weber syndrome<sup>2</sup>, it has been included in this discussion.

As with Klippel-Trenaunay syndrome Parkes Weber syndrome is characterised by capillary, and venous malformations with enlargement of limbs, in addition to significant arteriovenous fistulas. This may result in cutaneous lesions having a less cyanotic appearance than those found in Klippel-Trenaunay syndrome.<sup>27</sup> Lymphatic malformations are only very rarely seen and this can be used to distinguish between the two disorders. Upper limb involvement occurs in 23% of cases compared to 5% in Klippel-Trenaunay syndrome. Because of the higher incidence of malformations with high flow rates there is an increased risk of cardiac failure and limb ischaemia, indicating a need to clearly differentiate the two syndromes.<sup>12,27</sup>

### 6. Conclusion

Although neurocutaneous disorders are rarely encountered in forensic practice, occasional case will present for autopsy due to their association with sudden and unexpected death. Even in cases with established diagnoses there may be no way to determine whether death has been due to epilepsy, intracranial haemorrhage or pulmonary thromboembolism without a full autopsy. Unfortunately, variable terminology, overlapping features and inexact application of diagnostic criteria also means that cases presenting to autopsy may not have been accurately classified during life. This may make the autopsy assessment extremely important, particularly if there is a heritable component to the condition. A possible autopsy approach to cases is summarised in Table 3.

## **Conflict of Interest**

None declared.

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None

## **Ethical Approval**

Not applicable.

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