

Intracranial Aneurysms in Klippel-Trenaunay/ Weber Syndromes: Case Report

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Received, January 2, 2009.

Accepted, November 27, 2009.

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OBJECTIVE: We present a comprehensive review of intracranial aneurysms in Klippel-Trenaunay and Klippel-Trenaunay-Weber syndromes (KTS/KTWS), and examine factors influencing the risks of surgery vs conservative management.

CLINICAL PRESENTATION: A 58-year-old physician with KTS affecting the right extremities presented with left hemispheric cerebellar stroke and was discovered to harbor four intracranial aneurysms of the posterior circulation: fusiform mid- and distal BA (2.6 × 2 × 2 cm), fusiform right proximal P1 (2 × 1.3 × 1.3 cm), fusiform right distal P1 (2.8 × 2.7 × 2 cm), and saccular left distal posterior inferior cerebellar artery (2.5 × 2.5 × 2.5 cm). Ten years later he had an infarct in the paramedian distribution of the basilar artery and a right internal capsule stroke. Two months later, he developed hydrocephalus, ultimately presenting in status epilepticus 4 months later secondary to ongoing aneurysm expansion and mass effect.

INTERVENTION: Systemic anticoagulation for acute thrombosis with possible distal arterioarterial embolization from giant P1 aneurysms. Ventriculoperitoneal shunting for hydrocephalus. The patient died within 9 days after admission and 10 years after the initial discovery of aneurysms.

CONCLUSION: Strict control of modifiable risk factors compromising vascular integrity and periodic neuroimaging are warranted in KTS/KTWS patients. KTS/KTWS patients are hypercoagulable, and may be predisposed to aneurysm thrombosis with increased risk for distal arterial microembolization. Stroke-related morbidity secondary to distal arterioarterial aneurysm thrombus embolization and acute aneurysm thrombosis may be decreased with systemic anticoagulation in this patient population. KTS/KTWS patients have significantly higher rates of DVT and PE than the general population, and should be classified in the high-risk category for venous thromboembolism prophylaxis. Both endovascular and open cerebrovascular techniques have been used successfully in KTS/KTWS patients with intracranial aneurysms.

KEY WORDS: Cerebrovascular accident, Giant intracranial aneurysm, Hydrocephalus, Intracranial embolism and thrombosis, Klippel-Trenaunay-Weber Syndrome, Seizures, Status epilepticus

Neurosurgery 66:E1027-E1028, 2010

DOI: 10.1227/01.NEU.0000368392.69904.BE

www.neurosurgery-online.com

Little is known regarding intracranial aneurysms in Klippel-Trenaunay and Klippel-Trenaunay-Weber syndromes (KTS and KTWS, respectively). Only 7 cases have been published previously.¹⁻⁷ In the first comprehensive review of KTS/KTWS and intracranial aneurysms, we report the case of our colleague with Klippel-Trenaunay-Weber Syndrome who died of complications of multiple giant intracranial aneurysms at the age of 58,

in an effort to decrease aneurysm-associated morbidity and mortality for future patients with this disorder, and to underscore the importance of future case reports and research elucidating the pathophysiological mechanisms of vascular compromise and subsequent aneurysm formation in this unique spectrum of disorders. Features of KTS and KTWS influencing management decisions with regard to unruptured intracranial aneurysms, including hypercoagulability, thromboembolism, and coagulopathy are discussed, including treatment recommendations for pre-, intra-, and postoperative antithrombotic prophylaxis and management of coagulation parameters. A comprehensive review of previously reported cases of neurosurgical treatment of intracranial aneurysms in KTS/KTWS is provided, including techniques and outcomes.

ABBREVIATIONS: KTS, Klippel-Trenaunay syndrome; KTWS, Klippel-Trenaunay-Weber syndrome; DVT, deep vein thrombosis; PE, pulmonary emboli; PICA, posterior inferior cerebellar artery; AV, arteriovenous; VP, ventriculoperitoneal; PCA, posterior cerebral artery; BAA, basilar artery aneurysm; SCA, superior cerebellar artery; BA, basilar artery.

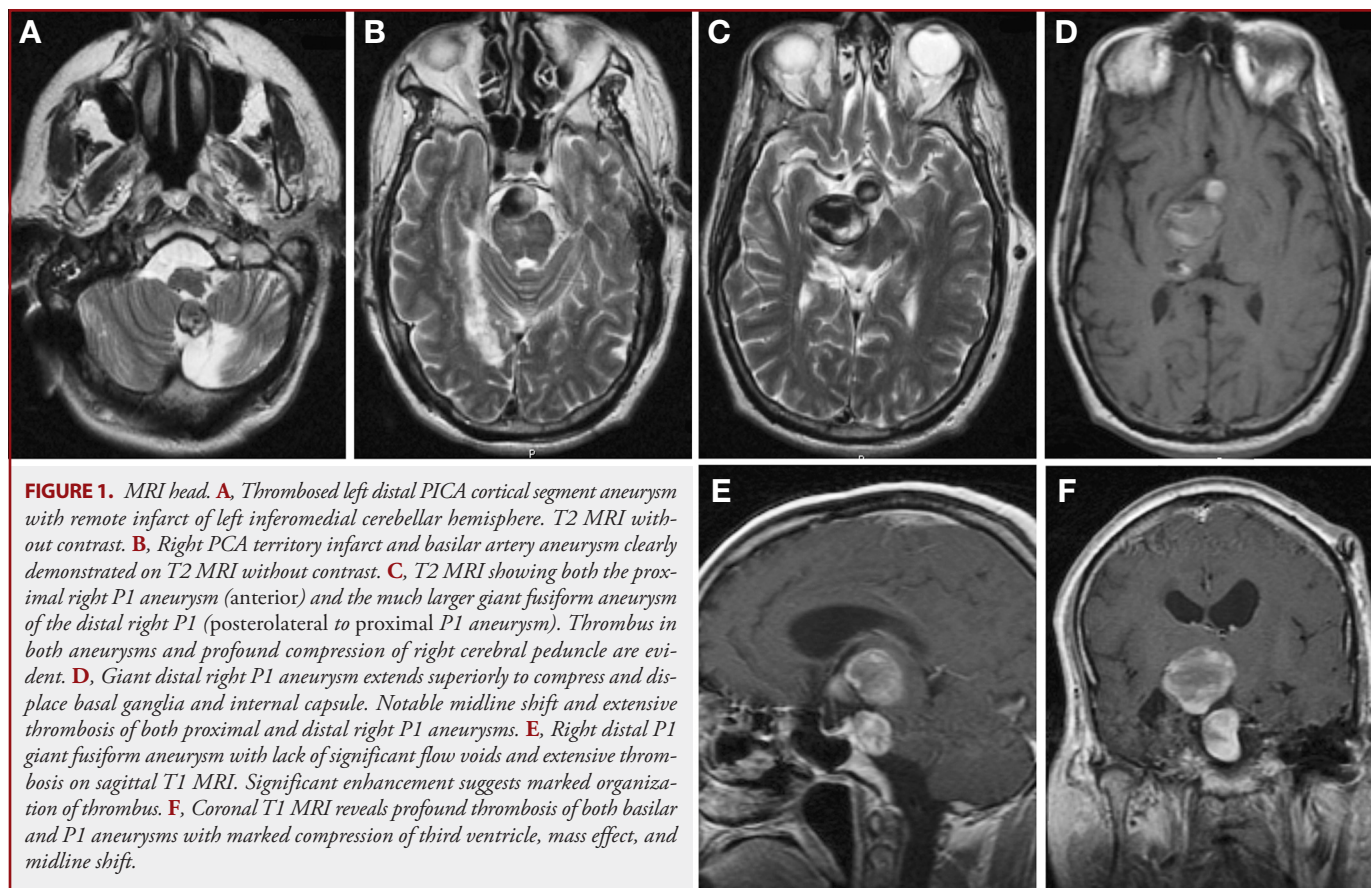


FIGURE 1. MRI head. **A**, Thrombosed left distal PICA cortical segment aneurysm with remote infarct of left inferomedial cerebellar hemisphere. T2 MRI without contrast. **B**, Right PCA territory infarct and basilar artery aneurysm clearly demonstrated on T2 MRI without contrast. **C**, T2 MRI showing both the proximal right P1 aneurysm (anterior) and the much larger giant fusiform aneurysm of the distal right P1 (posterolateral to proximal P1 aneurysm). Thrombus in both aneurysms and profound compression of right cerebral peduncle are evident. **D**, Giant distal right P1 aneurysm extends superiorly to compress and displace basal ganglia and internal capsule. Notable midline shift and extensive thrombosis of both proximal and distal right P1 aneurysms. **E**, Right distal P1 giant fusiform aneurysm with lack of significant flow voids and extensive thrombosis on sagittal T1 MRI. Significant enhancement suggests marked organization of thrombus. **F**, Coronal T1 MRI reveals profound thrombosis of both basilar and P1 aneurysms with marked compression of third ventricle, mass effect, and midline shift.

KTS is a rare sporadic congenital mesodermal phakomatosis typically diagnosed in childhood.⁸⁻¹³ First described in 1900 by Maurice Klippel and Paul Trenaunay,¹⁴ this uncommonly encountered neurocutaneous syndrome presents with the triad of cutaneous capillary malformations, venous malformations, and bone and soft tissue hypertrophy.¹⁵⁻³⁶ The closely related Klippel-Trenaunay-Weber syndrome (also known as Parkes-Weber syndrome) consists of the KTS triad plus arteriovenous (AV) fistula.^{15,16,18,25,27,29,31,37-42} Some believe that the Klippel-Trenaunay syndromes are a continuum, with KTWS lying in the severe grade vascular malformation range.^{42,43} However, a progression from KTS to KTWS has yet to be documented in the literature. Nonetheless, it should be noted that the AV fistula associated with Klippel-Trenaunay-Weber syndrome confers a more unfavorable prognosis.²⁷

Convincing evidence regarding the precise etiology of KTS remains elusive, although, in the years since its discovery, a variety of theories have been advanced.^{15,17,23,32,35,42,43,45-50} Current evidence most strongly supports a mesodermal abnormality in early fetal development as a unifying etiology underlying the triad of malformations in cell lineages derived from the mesoderm: hemangioblastic, lymphoblastic, and osteoblastic.^{17,18,27,51,52} The appeal of a mesodermal explanation lies in its ability, unlike a vascular etiology, to account for the other congenital malformations

often seen in association with KTS. Klippel-Trenaunay syndrome (and the related Klippel-Trenaunay-Weber syndrome), although congenital, are not thought to be hereditary.^{27,28} However, it has been suggested that KTS may be a paradominant disorder wherein two “hits” to susceptibility genes may be required to develop the KTS phenotype.⁵³⁻⁵⁵ Promising molecular studies on potential gene candidates are currently being conducted.^{54,56-59}

CASE REPORT

A 58-year-old white male with Klippel-Trenaunay syndrome (right upper and lower extremity hypertrophy, right upper extremity venous varicosities, and right palmar and temporal capillary hemangiomas), hypertension, and hypercholesterolemia presented to the hospital in status epilepticus.

Ten years prior to admission, the patient suffered an infarct in the distribution of the left posterior inferior cerebellar artery (PICA) secondary to acute thrombotic occlusion of distal left PICA aneurysm (Figure 1A), resulting in gradual onset of left hemiparesis, with residual ataxia and vertigo. The region of infarct in the inferomedial left cerebellar hemisphere is evident on MRI (Figure 1A). Neuroimaging at that time additionally revealed a giant fusiform mid and distal basilar artery aneurysm extending to involve the entire P1 segment of the right posterior cerebral artery (Figure 1-3). Close neurosurgical follow-up with imaging of aneurysms demonstrated progressive enlargement

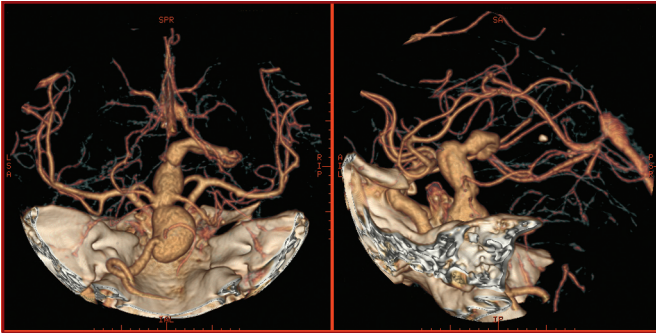


FIGURE 2. Computed tomographic angiography head. Axial (left) and coronal (right) views allow visualization of circle of Willis and posterior circulation. Filling defect in thrombosed portion of distal right P1 aneurysm is evident.

over ensuing years. Patient had a high-surgical risk and declined neurosurgical intervention.

Six months before admission, the patient had a second infarct, this time in the paramedian distribution of the basilar artery, at the left caudal pons, resulting in a left facial CN VII palsy (Figure 4I). Several weeks later, a third infarct, of the posterior internal capsule, resulted in dense left-sided hemiparesis, associated sensory loss, left Babinski, anisocoria (OD 3 mm, OS 4 mm) with a left afferent pupillary defect and left homonymous hemianopsia with full extraocular movements, intact conjugate gaze, and no nystagmus (Figure 1B–D). Neuroimaging was consistent with acute aneurysm thrombosis and distal arterioarterial embolization from aneurysm for which anticoagulation was initiated. Prior to anticoagulation, no coagulation abnormalities were detectable with standard coagulation panel (platelets, prothrombin time, partial thromboplastin time, international normalized ratio), although a hypercoagulability workup was not performed. Patient was discharged to an inpatient physical rehabilitation facility.

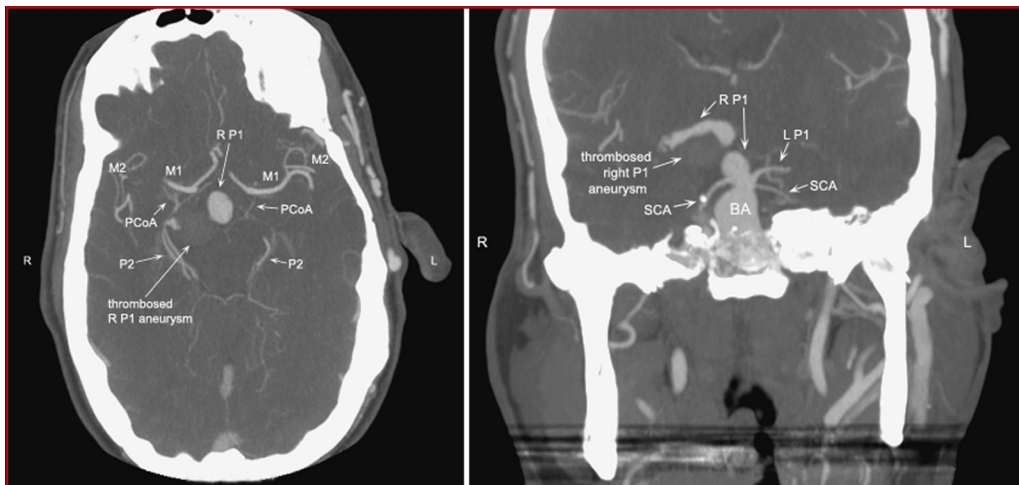


FIGURE 3. Three-dimensional computed tomographic angiography anterior/posterior (left) and lateral (right) views demonstrate a giant fusiform aneurysm of the mid and distal basilar artery. A second large aneurysm (superior to SCAs) of the proximal right P1 is evident. A segment of P1 of normal caliber is seen leading to a third giant aneurysm (distal right P1). The entire aneurysm is not visible on computed tomographic angiography because of thrombosis of the inferior aspects. Consequently, distal right P1 appears fusiformly ectatic.

Two months later, the patient was admitted to the neurosurgery service for obstructive hydrocephalus secondary to compression of ventricular outflow tract (third ventricle) by giant fusiform distal right P1 aneurysm (suggesting ongoing and acute expansion of aneurysm) (Figure 1F, G) for which he underwent ventriculoperitoneal (VP) shunting. At that time, a slight tongue deviation to the left was noted. Proximity of VP shunt placement to area postrema resulted in chronic nausea and vomiting that was poorly controlled with antiemetics.

Four months after VP shunting, the patient was brought to the emergency department in status epilepticus (current admission), where he was stabilized and intubated; anticonvulsants were administered. The patient was admitted to the neurosurgical intensive care unit and remained on ventilator support, subsequently developing cardiac tamponade and aspiration pneumonia. The patient was DNR (do not resuscitate) and although he was sedated, he was responsive and expressed agreement when his wife indicated on admission day 5 that he would wish to be extubated.

Palliative care was initiated. The patient died 4 days later, 9 days after admission and within 10 years of initial aneurysm presentation and diagnosis.

GROSS NEUROPATHOLOGICAL FINDINGS

A giant fusiform aneurysm of the mid and distal basilar artery measuring $2.6 \times 2 \times 2$ cm originated 1.4 cm distal to the vertebrobasilar junction and extended to the basilar apex (Figure 4A). A very large fusiform aneurysm of the proximal right P1 measured $2 \times 1.3 \times 1.3$ cm and originated at the right basilar-PCA junction, extending 2 cm superiorly toward the optic chiasm (Figure 4A, D). Transverse sections of the basilar and proximal P1 aneurysms revealed intraluminal postmortem thrombus (Figure 4E). A giant aneurysm of the right distal P1 causing marked compression of the right thalamus, third ventricle, and right lateral ventricle with midline shift to the left and distortion of the right internal capsule measured $2.8 \times 2.7 \times 2$ cm and communicated with the proximal right P1 aneurysm via a 1-mm segment of P1 of normal caliber (Figure 4K). Complete occlusion of the inferior half of the distal P1 aneurysm with well-organized thrombus was evident, whereas the superior half of the aneurysm contained intraluminal thrombus consistent with postmortem formation (Figure 4K). An area of recent (≤ 6 months) hemorrhagic infarct was noted in the region of the thalamus, hippocampus, and internal capsule on the right (Figure 4L), as well as a region of infarct in the distribution of the right PCA extending to the inferior occipital lobe (Figure 4M).

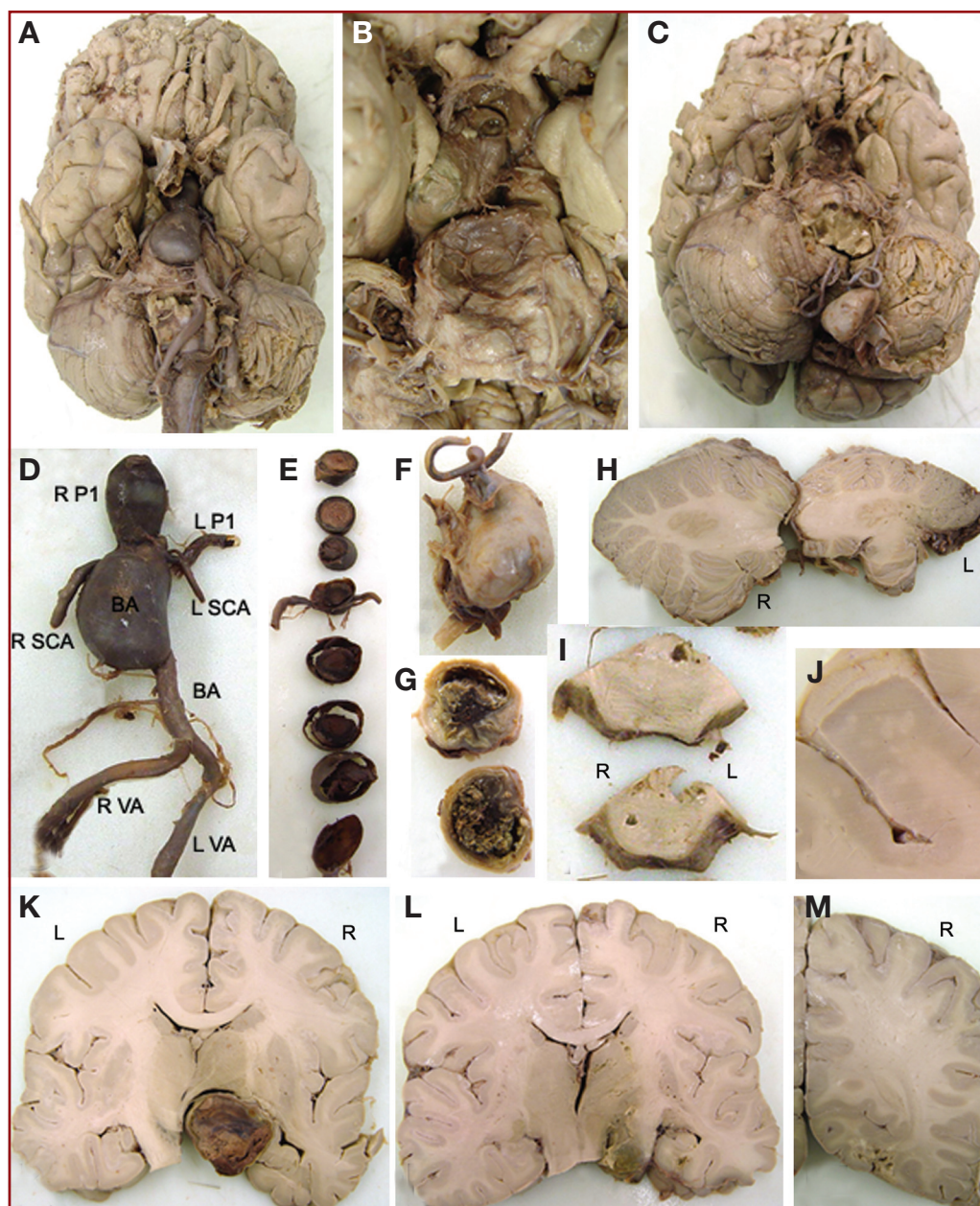


FIGURE 4. **A,** Giant fusiform basilar artery aneurysm evident along ventral aspect of brainstem. Also visible is aneurysm of right proximal P1. **B,** Removal of circle of Willis. Profound compression of pons. Marked widening and deepening of basilar groove. Distal right P1 aneurysm visible immediately medial to right uncus. **C,** Aneurysm of left distal PICA, cortical segment. **D,** Posterior circulation. BA and proximal right P1 fusiform aneurysms. **E,** Transverse sections of BA and proximal right P1 aneurysms. SCAs seen exiting BAA at near basilar apex. Aneurysm above SCAs is proximal right P1 aneurysm. **F,** Saccular giant distal left PICA aneurysm. **G,** Cross section of PICA aneurysm reveals well-organized thrombus with mural calcification. **H,** Remote infarct of left cerebellar hemisphere (at right side of image), with diffuse hemispheric atrophy. Shown to the left is right cerebellar hemisphere for comparison. **I,** Caudal pons. Left anterior cystic remote infarct in paramedian distribution BA. Right corticospinal tract degeneration secondary to infarct of right internal capsule. **J,** White matter heterotopia in region of left supramarginal gyrus. **K,** Distal right P1 giant fusiform aneurysm with compression of thalamus, third ventricle, and midline shift. **L,** Subacute infarct of right internal capsule, hippocampus, thalamus, in distribution of right PCA. **M,** Extension of right PCA infarct to occipital lobe.

The aneurysm walls of the basilar and PCA aneurysms were thin and hypocellular with intimal hyperplasia and organizing luminal thrombosis. The aneurysm wall of the PICA aneurysm was thickened with disorganized smooth muscle cells and well-organized luminal thrombus with dystrophic calcification and cholesterol deposits. Inflammation was notable in all aneurysms.

Profound compression by BAA of the pons and midbrain was noted, with marked widening and deepening of the basilar groove (Figure 4B). An area of hemorrhagic infarct in the left anterior aspect of the caudal pons extended inferiorly as a cavitating lesion consistent with remote infarct in the paramedian distribution of the mid-basilar artery (Figure 4I). Cystic cavitation of the right corticospinal tract within the caudal pons was consistent with degeneration of right corticospinal tract secondary to right internal capsule infarct (Figure 3J).

A giant saccular aneurysm of the left distal PICA cortical segment measuring $2.5 \times 2.5 \times 2.5$ cm was evident (Figure 4C, F) with cystic cavitation and diffuse atrophy of the supplied left cerebellar hemisphere compared with the right (Figure 4H). PICA aneurysm revealed well-organized thrombus with mural calcification (Figure 4G).

DISCUSSION

Review of Published Cases of Intracranial Aneurysm Associated with Klippel-Trenaunay/Weber Syndrome

Arterial aneurysms in KTS and KTWS are rare—only 14 cases have been reported previ-

ously.^{1-4,6,7,60-66} A case of carotid artery dissection has also been reported, suggesting a diffuse vascular pathology in KTS that may involve diminished integrity of arterial vessels and confer susceptibility both to aneurysm formation as well as dissection.⁶⁷ Congenital weakness of at least the venous vasculature in KTS has been previously suggested.⁶⁸ Cerebral AV fistula associated with KTSW has also been reported, in some cases associated with seizure activity.^{3,69}

It is estimated that fewer than 10% of patients with Klippel-Trenaunay syndrome exhibit (noncutaneous) vascular involvement of the head and neck.⁷⁰ Only 7 cases of intracranial arterial aneurysms associated with Klippel-Trenaunay syndrome/Klippel-Trenaunay-Weber syndrome have been reported previously (Table 1).¹⁻⁷ Table 2 summarizes and compares the features, presentation, and neurosurgical approaches and outcomes for cases of intracranial and giant aneurysms in patients with KTS/KTWS.

Open Cerebrovascular Treatment of Vascular Malformations in Klippel-Trenaunay Syndrome

Oyesiku et al⁷¹ reported successful obliteration of a cerebral arteriovenous fistula in a 12-week-old patient with Klippel-Trenaunay-Weber syndrome via craniotomy and clip placement.

Taira et al (reviewed in Table 1) reported successful clipping of an 18 × 15 × 20 mm saccular aneurysm of the MCA-M1 origin in an 8-year-old KTS patient who presented with subarachnoid hemorrhage. The patient's intra- and postoperative course was uneventful and no morbidity was reported.⁷

Review of the literature did not yield additional reports of successful open cerebrovascular clipping of intracranial arterial malformations in Klippel-Trenaunay/Klippel-Trenaunay-Weber syndromes. However, it is anticipated that, with the potential exception of a comorbid chronic coagulopathy, KTS patients are excellent candidates for open cerebrovascular procedures given their young age and relative lack of comorbidities that would elevate neurosurgical risk.

Endovascular Treatment of Vascular Malformations in Klippel-Trenaunay Syndrome

Szajner et al⁶⁶ report successful embolization of a large aneurysm at the origin of the thyrocervical trunk in a patient with KTS via an arterial approach with a mixture of *N*-butylcyanoacrylate and Lipiodol (one-third *N*-butylcyanoacrylate, two-thirds Lipiodol). Intra- and postoperative course was unremarkable. The patient received steroids for 4 days postoperatively and complete thrombosis of the aneurysm was confirmed at 6 months follow-up.

Yamagami et al⁷² reported successful microcoil embolization of a congenital extrahepatic portosystemic venous shunt in a 6-year-old patient with Klippel-Trenaunay-Weber syndrome.

Natterer et al⁷³ successfully embolized the left superior and middle rectal arteries with platinum microcoils in an 8-year-old patient with KTS.

Alexander et al⁷⁴ described successful embolization with polyvinyl alcohol particles and *n*-butylcyanoacrylate of the right thyrocervical

trunk and left T2, left T4, and right T4 intercostal arteries feeding a right paraspinal extradural AVM in a patient with Klippel-Trenaunay-Weber syndrome without postoperative morbidity.

Nakstad et al⁷⁵ reported successful embolization of an intradural extramedullary spinal arteriovenous fistula with platinum coils in a 13-year-old patient with KTWS, requiring three sessions, without postinterventional morbidity, and with dramatic resolution of preinterventional symptoms.

De Blasi et al (reviewed in Table 1) reported successful balloon occlusion of the right vertebral artery and coil embolization of the left vertebral artery during two separate procedures in a patient with a giant basilar artery aneurysm and distal right vertebral artery aneurysm and Klippel-Trenaunay syndrome.² No morbidity was reported in association with the procedures and, although the patient did not regain previous neurological losses associated with putative brainstem infarction secondary to aneurysm compression, future potential infarcts related to aneurysm expansion and hemorrhage were likely avoided, especially considering the age of the patient (26 years old) and consequent cumulative lifetime-associated risk of aneurysm expansion and rupture.

Coagulopathy in KTS/KTWS

Vascular malformations, such as those seen in Klippel-Trenaunay syndrome, may become a source of platelet sequestration and fibrinogen consumption, with a bleeding diathesis ensuing as a result of chronic localized intravascular consumptive coagulopathy.^{22,32,76-80} This, in turn, may progress to disseminated intravascular coagulation following trauma (especially to the affected limb), surgical intervention, or bedside procedures.⁸¹⁻⁸⁵ Acute changes in coagulation status in response to surgical procedures have also been reported,⁸⁵ suggesting that close monitoring of coagulation parameters may be warranted postoperatively in this particular patient population.

Chronic coagulopathy in KTS may have an adverse impact on response to neurosurgical interventions such as embolization. In patients with chronic coagulopathy secondary to venous malformation, no adverse effect on coagulation profiles was observed following embolization with platinum microcoils.⁸⁶ However, for severe preoperative coagulopathy, correction of coagulation parameters is advisable to reduce risk of intra- and postoperative hemorrhage, as well as to ensure adequate thrombotic response to embolization. Mason et al⁸⁶ reported successful embolization in patients with marked coagulopathy secondary to a venous malformation following preoperative prophylaxis with cryoprecipitate, platelets, or fresh-frozen plasma to facilitate thrombosis. However, in cases of severe coagulopathy that cannot be corrected, embolization may be inadvisable.⁸⁶

Platelet levels in our patients were within normal limits. This finding is not unusual in patients with coagulopathy secondary to venous malformations, wherein depletion of coagulation factors rather than platelets is typically observed.⁸⁷ Consequently, a coagulation panel including prothrombin time and partial throm-

TABLE 1. Published Reports of Intracranial Aneurysms Associated With Klippel-Trenaunay and Klippel-Trenaunay-Weber Syndrome^a

Authors, Year	Patient	KTS ^b	Presentation	Diagnosis	Aneurysm(s)	Intervention	Outcome
Alberti, 1976	25, M	Right	HA, vomiting, R hemiparesis, anisocoria (L>R), nystagmus, R CN VI palsy, L CN VII nuclear paralysis, dysarthria, dysphagia, salivation, somnolence	Thrombotic occlusion BAA with subsequent infarct (lower pons & medulla)	Aneurysmal dilatation distal basilar, ectasia right vertebrabasilar junction	None	Residual occipital HAs, nystagmus, R CN VI palsy, ↑DTRs R, ataxia R
Effer & Sachs, 1979 ^c	40, M	Right	Age 12: generalized seizures	Epilepsy	None	None	Not reported
			Age 21: acute spastic R hemiparesis with motor aphasia and xanthochromic CSF	Hemorrhagic left infarct	None	None	Full recovery of neurological function
			Age 40: severe HA, diplopia, generalized epileptic seizures, xanthochromic CSF	Aneurysm expansion with hemorrhage	Saccular R PCA, Saccular R OphA, 3 giant saccular aneurysms L carotid siphon with AV-fistula, fusiform ectasia extracranial ICA	None	Attempted suicide; recurrent CVAs, otherwise not reported
Goldstein et al., 1984	24, WF	Left	Severe L occipital recurrent HAs with associated nausea and photophobia	Recurrent migraine or vascular HA	Multiple aneurysmal dilatations with calcification of anomalous L PCA-P1/L PCoA collateral vessel compensating ipsilateral ICA agenesis	None	Neurologically stable at 1.5 years follow-up
Taira et al., 1991	8, M	Right	Prodromal HAs, somnolence, meningismus	SAH	18 × 15 × 20 mm saccular aneurysm at M1 MCA origin	Surgical clipping	Full recovery, no residual morbidity
Spallone & Tcherkayev, 1996	28, F	Right	HA, progressive L hemiparesis	Epilepsy, congenital psychomotor retardation, hemiparesis due to multiple meningiomas and cranial hyperostosis	Fusiform intracavernous R ICA aneurysm	Resection of meningiomas, cranioplasty for hyperostosis	Resolved hemiparesis with residual ↑DTRs, in "good health" at 2 years follow-up
Ouellet et al., 1997 ^c	27, M	Left	R hemiparesis w/sensory loss & ↓pain sensation, R UE dysmetria, R ↑reflexes, R Babinski, R facial weakness & sensory loss, ↓gag, bilat. tongue weakness, dysarthria, drooling, NV, retro-orbital pain, diplopia, nystagmus	Complete acute thrombosis of fusiform basilar artery aneurysm, ischemic left pontine infarct	Fusiform basilar artery aneurysm, huge left common iliac artery aneurysm, 1.5 cm bilobed left renal artery aneurysm, small superior mesenteric artery aneurysm	Anticoagulation, hypervolemic hemodilution, pharmacologic hypertension	Residual mild R hemiparesis, partial resolution pontine infarct, partial recanalization lower portion BAA, recurrent brainstem ischemia SX
De Blasi et al., 2000	26, WM	Left	Vertigo, progressive L hemiparesis, L lateral gaze palsy with nystagmus, palate droop, absent gag reflex, L hyperreflexia, bilateral Babinski	Compression and displacement of brainstem to left	Giant basilar artery aneurysm, distal R vertebral artery aneurysm	R VA occlusion (balloon), L VA occlusion (coils)	No recovery, no morbidity from procedure

Continues

TABLE 1. Continued

Authors, Year	Patient	KTS ^a	Presentation	Diagnosis	Aneurysm(s)	Intervention	Outcome
Star et al., 2010 ^c	58, WM	Right	Age 48: gradual onset mild L hemiparesis, ataxia, vertigo	L inferomedial cerebellar infarct (distal PICA-cortical segment territory)	2.6 × 2 × 2 cm fusiform distal BA/2 × 1.3 × 1.3 cm fusiform proximal R P1/2.8 × 2.7 × 2 cm fusiform distal R P1/2.5 × 2.5 × 2.5 cm saccular distal L PICA	None	Residual ataxia and vertigo
			10 years later: L hemiparesis, L sensory loss, L Babinski, anisocoria (OD 3 mm, OS 4 mm), L afferent pupillary defect, L homonymous hemianopsia	R PCA infarct involving R internal capsule, R thalamus, R hippocampus, R optic tract	Same	Anticoagulation, inpatient rehabilitation only	Resolution of visual and sensory defects only
			2 months later: HA, altered mental status, L tongue deviation	Aneurysm expansion, hydrocephalus	Same	VP shunt	Resolution of hydrocephalus, onset shunt-related nausea & vomiting
			4 months later: status epilepticus	Status epilepticus secondary to aneurysm expansion and mass effect	Same	Anticonvulsants, intubation, admit neuro-surgical ICU, ventilator support	Cardiac tamponade, aspiration pneumonia, death following extubation in accordance with DNR support

^a KTS, Klippel-Trenaunay syndrome; M, male; HA, headache; R, right; L, left; CN, cranial nerve; BAA, basilar artery aneurysm; DTR, deep tendon reflex; CSF, cerebrospinal fluid; PCA, posterior cerebral artery; OphA, ophthalmic artery; AV, arteriovenous; ICA, internal carotid artery; CVA, cerebrovascular accident; WF, white female; PCoA, posterior communicating artery; SAH, subarachnoid hemorrhage; MCA, middle cerebral artery; F, female; UE, upper extremity; NV, nausea and vomiting; SX, symptoms; WM, white male; VA, vertebral artery; PICA, posterior inferior cerebellar artery; BA, basilar artery; OD, oculus dexter; OS, oculus sinister; VP, ventriculoperitoneal; ICU, intensive care unit; DNR, do not resuscitate.

^b All studies were case reports.

^c Refers to lateralization of Klippel-Trenaunay/Klippel-Trenaunay-Weber syndrome symptoms.

boplastin time is recommended to adequately monitor coagulation status pre- and postoperatively in patients with KTS/KTWS.

Venous Thromboembolism and Deep Venous Thrombosis in KTS/KTWS

Hypercoagulability secondary to venous malformations is well established.^{84,86,88} Klippel-Trenaunay syndrome is associated with an increased risk of deep venous thrombosis (DVT) and thromboembolism.^{28,44,67,89-91} The incidence of thromboembolic complications in KTS is estimated to be as high as 17 to 22%, and postoperative thromboembolism may be as high as ten times that seen in non-KTS patients.^{28,44,92} Pulmonary emboli (PE) as a complication of KTS are also well documented.^{25,28,44,87,89,93-104} Increased susceptibility to PE and DVT warrants classification of KTS/KTWS patients at high risk for post- and intraoperative venous thromboembolism.

DVT/PE Prophylaxis in KTS/KTWS Patients with Intracranial Aneurysms

Treatment recommendations regarding anticoagulation in KTS patients are largely based on case reports. Aggressive intra- and postoperative DVT prophylaxis has been recommended.⁹⁷ Conventional anticoagulation therapy for hypercoagulability in KTS has proven disappointing.⁸⁷ Although anticoagulation is reportedly successful in managing some cases of KTS-associated PE,^{96,99} in other cases, patients developed PE despite being anticoagulated at the time of onset.^{97,98} Warfarin and unfractionated heparin are reported to be less effective than low-molecular-weight heparin.¹⁰⁵ Gianlupi et al recommend anticoagulation with warfarin to an international normalized ratio of 3 to 4 and inferior vena caval filter placement for long-term throm-

TABLE 2. Characteristics of Klippel-Trenaunay/Weber Syndrome Patients With Intracranial Aneurysms

	All Intracranial Aneurysms (n = 8)	Giant Intracranial Aneurysms (n = 3)
Average age at diagnosis, y	28	38
Sex		
Male	75%	100%
Female	25%	
Symptom lateralization		
Right	63%	67%
Left	37%	33%
Most common presenting symptom	Headache 88%	Mass effect 100%
	Thrombosis 38%	Headache 67%
	Mass effect 38%	Thrombosis 33%
	Hemorrhage 25%	Hemorrhage 33%
Hemiparesis	75%	100%
Visual disturbance	75%	100%
Hydrocephalus	13%	33%
New-onset seizures ^a	25%	33%
Aneurysm-related infarcts	50%	67%
Anterior/posterior circulation aneurysm(s) ^b		
Anterior	38%	33%
Posterior	75%	67%
Anterior circulation aneurysm locations ^b	67% ICA	100% ICA
	33% Ophthalmic	
	33% MCA	
Posterior circulation aneurysm locations ^b	67% Basilar	100% Basilar
	50% PCA	50% PCA
	17% Vertebrals	50% PICA
	17% VB junction	
	17% PICA	
Avg number intracranial aneurysms/patient	2.4	3.7
Highest/lowest number aneurysms/patient	5/1	5/2
Neurosurgical intervention attempted	25%	33%
Average age at treatment, y	17	26
Neurosurgical approach	50% Endovascular	
50% Open	100% Endovascular	
Neurosurgical approach morbidity	0% Endovascular	0% Endovascular
	0% Open	
Recovery rate ^c	0% No intervention	0% No intervention
	50% Intervention	0% Intervention

^a One patient had pre-existing seizure disorder.

^b Some patients had multiple aneurysms, giving a total greater than 100%.

^c Any neurological recovery

boembolism prophylaxis.⁹⁷ However, inferior vena caval filters are only effective if the vascular malformation is in the lower extremity. In light of current evidence regarding hypercoagulability, the

use of oral contraceptives and other prothrombotic agents in KTS/KTWS patients with intracranial aneurysms, especially giant intracranial aneurysms, should be strongly reconsidered.^{28,44,97}

Intracranial Aneurysm Thrombosis and the Role of Anticoagulation in KTS/KTWS

Thromboembolus formation and propagation may be accelerated in KTS, posing consequences of concern for intracranial aneurysms, which may become a source of thrombosis or multi-embolic infarcts. This case, as well as the others reviewed (Table 1), demonstrates that acute thrombosis of intracranial aneurysms in KTS/KTWS is a source of morbidity in this patient population and therefore may mandate more extensive coagulation studies including heritable prothrombotic mutations. On the other hand, evidence of previous thrombosis may be sufficient for empiric anticoagulation.

Of the 8 published cases of intracranial aneurysms associated with KTS/KTWS (including ours), only two involved anticoagulation for thrombosed aneurysms. In our case, anticoagulation with warfarin was initiated following a second stroke secondary to acute thrombosis of two giant P1 aneurysms with possible distal arterioarterial embolization. No thrombus progression was detected on subsequent neuroimaging. Therapy was not initiated after the first infarct because of acute thrombosis of distal PICA aneurysm with subsequent left hemispheric cerebellar stroke (at outside institution). Although no hemorrhagic complications related to anticoagulation were encountered, our patient only survived for 6 months.

The case reported by Ouellet et al is the second case of KTS/KTWS associated intracranial aneurysm with acute thrombosis in which anticoagulation was instated.⁵ The authors did not report which anticoagulant was used. However, no subsequent additional thrombosis of the aneurysm was noted during 2 years of follow-up while on anticoagulation therapy, and, in fact, limited recanalization of both aneurysms was noted.

In neither our case nor the case of Ouellet et al were there any hemorrhagic complications related to aneurysm rupture or intracranial hemorrhage. However, length of follow-up was limited in both cases. Further evidence is clearly necessary to firmly establish the risk vs benefit of anticoagulation therapy in KTS/KTWS patients with intracranial aneurysms. However, preliminary evidence from our study and others suggests anticoagulation may play an important role in neurosurgical management of KTS/KTWS patients with intracranial aneurysms, especially those undergoing neurosurgical procedures or who have a history of embolic or thrombotic infarcts.

CONCLUSION

Our conclusions are limited by sample size, and further study is required to elucidate optimal neurosurgical management of this patient population. However, preliminary evidence from these illustrative cases, including our own, suggests that (1) strict control of modifiable risk factors compromising vascular integrity and periodic neuroimaging are warranted in KTS/KTWS patients. (2) KTS/KTWS patients are hypercoagulable, and may be predisposed to aneurysm thrombosis with increased risk for distal arterial microembolization. (3) Stroke-related morbidity second-

ary to distal arterioarterial aneurysm thrombus embolization and acute aneurysm thrombosis may be decreased with systemic anticoagulation in this patient population. (4) KTS/KTWS patients have significantly higher rates of DVT and PE than the general population, and should be classified in the high-risk category for venous thromboembolism prophylaxis. (5) Both endovascular and open cerebrovascular techniques have been used successfully in KTS/KTWS patients with intracranial aneurysms.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments

The authors wish to thank Eric M. Deshaies, MD, Assistant Professor of Neurosurgery, Director of Cerebrovascular, Skull Base, and Endovascular Neurosurgery, SUNY Upstate for neurosurgical consultation and Donald J. Jaeger, LFD, Technical Director of the Autopsy Service, Department of Pathology, SUNY Upstate for his assistance with photography of the gross neuroanatomic findings.

We dedicate this work to the patient, an accomplished physician, tireless professor, and gracious colleague, whose final request was to advance clinical awareness and management of intracranial aneurysms in Klippel-Trenaunay syndrome via publication of his case report, and without whose courage and dedication we could not have succeeded.

COMMENTS

The authors present an excellent review of Klippel-Trenaunay/Weber syndromes (KTS/KTWS) and management issues in the setting of intracranial aneurysm. Although the literature in this area is relatively small, the authors' effort is distinguished by its detailed review and their close association with the patient. When a patient with KTS presents with an intracranial aneurysm, should our management be any different from other patients with aneurysms of similar sizes? This report and the literature do not provide a great deal of evidence in this regard: the options for management of a KTS patient with a large intracranial aneurysm remain similar (endovascular vs open treatment of the aneurysm; handling of anticoagulation issues) to those non-KTS patients as well.

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The authors present a case of a patient harboring multiple intracranial aneurysms in the setting of Klippel-Trenaunay Syndrome. They emphasize that patients with KTS/KTWS are hypercoagulable and may be predisposed to aneurysm thrombosis and distal embolization. They suggest that anticoagulation may be useful in the prevention of aneurysm thrombosis and embolic complications. They also assert that these patients are at high risk for deep venous thrombosis and pulmonary embolus compared with the general population. Finally, they conclude that open cerebrovascular and endovascular techniques may be successfully utilized in the management of aneurysms in KTS/KTWS patients.

Characterization of cerebral aneurysms in patients with KTS/KTWS is clearly incomplete and the following report does provide additional information. Further investigation is needed to define the optimal treatment for cerebral aneurysms in patients with this condition and the present report does provide a framework for future focus.

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