

Case Report

Klippel -Trenaunay and Sturge -Weber overlapping syndrome in a Saudi boy

Amal Y Kentab

Division of Pediatric Neurology, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia

ABSTRACT

Sturge-Weber Syndrome (SWS) is a rare, sporadic neurocutaneous disorder. It is typically characterized by unilateral, posterior leptomeningeal angiomas that calcify, glaucoma, and facial portwine stains. Klippel-Trenaunay syndrome (KTS) is a rare congenital syndrome characterized by ipsilateral cutaneous capillary malformations, venous varicosities, and bony or soft tissue overgrowth of the affected limbs. The clinical, neuroradiological features as well as the outcome of a Saudi boy who was referred to the Division of Pediatric Neurology, King Saud University Medical City, Riyadh, Saudi Arabia, with intractable focal seizure and left-sided hemiparesis who was eventually diagnosed with combined SWS and KTS is described here. The rare

coexistence of SWS and KTS should be suspected in a child presenting with neurological manifestation such as epilepsy, mental sub normality, or hemiparesis, with port-wine staining or capillary hemangioma and enlarged limbs. Awareness may help in improving the quality of life and survival of these patients.

Keywords:

Cerebral angiomatosis; Cerebral calcification; Glaucoma; Klippel-Trenaunay-Weber syndrome; Sturge-Weber syndrome.

Correspondence to:

Dr. Amal Y Kentab

Division of Pediatric Neurology,
Department of Pediatrics (39)
King Saud University Medical City
College of Medicine, King Saud University
P.O. Box 2925, Riyadh 11461, Saudi Arabia
Fax: +966 (11) 469-1512
E-mail: amkentab@hotmail.com
E-mail: akentab@ksu.edu.sa

How to cite this article:

Kentab AY. Klippel -Trenaunay and Sturge -Weber overlapping syndrome in a Saudi boy. Sudan J Paediatr 2016;16(2):86 - 92.

INTRODUCTION

Sturge–Weber syndrome (SWS; OMIM 185300), is a sporadic, congenital neurocutaneous disorder affecting the cephalic venous microvasculature [1]. It has a frequency of 1 in 50,000 [2]. The hallmark anomaly is a capillary malformation affecting the brain and meninges (cerebral angiomas lesion of leptomeninges) with or without involvement of the choroid and/or episclera or conjunctiva and the skin [3]. The latter involves the skin of the face, typically in the ophthalmic (V1) and maxillary (V2) distributions of the trigeminal nerve. Hemangioma may also involve the mouth, pharynx and nasal mucosa or occur elsewhere in the body [1,4]. Klippel-Trenaunay Syndrome (KTS; OMIM 149000) first described in 1900 by Klippel and Trenaunay, is a rare neurocutaneous syndrome. It comprises a triad of port-wine stain or large cutaneous hemangiomas, varicose veins, and hypertrophy of the bones and or overlying soft tissue involving an extremity [5,6]. Neurological features as epilepsy, hemiparesis and mental retardation as well as visual disturbances occur if it is associated with SWS. Only a few cases of combined KTS and SWS have been reported in the literature. Not many cases have been in association with seizures. In order to highlight on this rare combination, this case report describes a coexistence of KTS and SWS in a Saudi boy who was referred because of intractable left- sided focal seizures. Physical examination revealed signs of glaucoma of the right eye, right hemi-hypertrophy with cutaneous hemangiomas, and left – sided hemiparesis. His focal seizures responded well to multiple antiepileptic drugs including phenobarbitone, carbamazepine, vigabatrin and topiramate.

Case Report

A 13-month -old boy was referred to the Division of Pediatric Neurology, King Saud University Medical City, Riyadh, Saudi Arabia with intractable focal

seizures, left hemiparesis and right-sided facial nevus since birth. He was born at term to consanguineous parents by emergency cesarean section because of failure to progress due to large weight and previous fetal loss. His mother had previous two 2nd trimester abortions, diagnosed with gestational diabetes and was kept on diet. He developed early neonatal seizures, and was started on phenobarbitone. He remained free of seizures until 5 months of age when he was admitted to a local hospital with fever, gastroenteritis, and breakthrough generalized tonic-clonic seizures lasting up to one minute, loaded with phenobarbitone, and discharged after 7 days of IV antibiotics. Since then he developed frequent focal seizures involving his right side, up to 7 times/ day lasting between few seconds to one minute, with respiratory compromise. Carbamazepine and clonazepam were added and partial response was achieved. At 10 months of age, he had another episode of fever, gastroenteritis and more frequent seizures mainly in the form of sudden duskiness of face, starring of eyes and holding breathing for 1-2 minutes with no clonic movement. Therefore, vigabatrin was added, and seizure frequency dropped from 6 times/week to once/month. He had global developmental delay, achieved mild head control at 7 months, rolled from side to side at 9 months, only cooing with intermittent social smile, and reduced personal- social interaction noted at 11 months. Physical examination revealed macrocephaly with head circumference 51 cm (>95th percentile), weight 10 kg (> 50th percentile), height 86 cm (> 95th percentile). He showed port-wine staining involving both sides of the his face, but more on right side, extending to the upper thorax, and right arm, wrist, extensor surface of hands and fingers as well as leg with right eye megalocornea, and buphthalmos indicating the presence of glaucoma (Figure 1).



Figure 1 – Shows relative macrocephaly, facial asymmetry, and bilateral facial nevus flammeus, more obvious on the right side.

He was also noticed to have right soft tissue hemihypertrophy involving the upper, and the lower extremities with clear difference in length of lower limbs (Figure 2). His neurological examination was significant for left lower facial weakness (upper motor neuron), left-sided hemiparesis with hypertonia and hyper-reflexia. Examination of his right eye, following urgent ophthalmology referral, showed buphthalmos, glaucoma with choroidal haemangioma and amblyopia. The rest of systemic examination was unremarkable. Cranial computerized tomography (CT) revealed generalized atrophy, more marked at the right cerebral hemisphere with right side dense gyriform calcification (Figure 3). Magnetic resonance imaging (MRI) of the brain with contrast showed

atrophy of the right cerebral hemisphere with thick cortex (Figure 3). There was also dilatation of supratentorial ventricular system left > right, minimal amount of left frontal subdural collection, prominent medullary vein in right cerebral hemisphere adjacent to the body of right ventricle, which drains to a prominent subependymal vein, enhancement of the surface of the right cerebral cortex (representing leptomeningeal angioma) and enlarged ipsilateral choroid plexus in trigon of right lateral ventricle. Magnetic resonance angiography (MRA) of the brain was normal, while magnetic resonance venography (MRV) revealed dilated medullary vein in right cerebral hemisphere. Electroencephalography (EEG) revealed asymmetrical background activity with clear reduced amplitude on the right hemisphere. Rare sharp waves were seen at the anterior, and middle part of left hemisphere. Brain auditory evoked potentials (BAEP), and electroretinogram (ERG) were normal bilaterally while visual evoked potential (VEP) revealed severe anterior optic pathway lesion bilaterally. Skeletal radiography revealed asymmetrical hypertrophy of the cranium, no skull calcification, and soft tissue hypertrophy with no bony overgrowth. Duplex ultrasound of lower limbs showed no evidence of peripheral ischemia. Abdominal ultrasonography showed no visceromegaly, and no deep organ venous malformation. Lower limbs magnetic resonance angiography (MRA) revealed asymmetrical left lower limb hypertrophy with normal symmetrical arteries, and no vascular malformation. Parental consent was taken for genetic study. He had a normal karyotype, and further mutational assessment for GNAQ, and VG5Q genes were not feasible for this patient. As the child had both features of Sturge-Weber syndrome and Klippel-Trenaunay syndrome, a diagnosis of an overlap syndrome was made. His medications were optimized, and he was free of seizures for 2 months then he got recurrence of right side clonic jerks 4 times/day, short lived lasting for few seconds with facial twitch,

circumoral cyanosis, and head deviation to right side. Topiramate was added, and vigabatrin was weaned off. The patient was re-evaluated by neurosurgeon and subdural-peritoneal shunt was done at 20 months of age to control the left frontal fluid collection, likely secondary to recurrent subdural hematoma. Aspirin was added, and he received dorzolamide (carbonic anhydrase inhibitor), timolol, and latanoprost for glaucoma followed by sclerectomy with mitomycin application and gradual decompression of his right eye under general anesthesia. His eye condition improved dramatically post-surgery and he continued on maintenance medications. He was also started on physical and occupational therapy. He was lost to follow-up at 24 months.



Figure 2 - Nevus flammeus involving the right upper limb, the wrist, and the extensor surface of fingers, with obvious soft tissue hypertrophy.

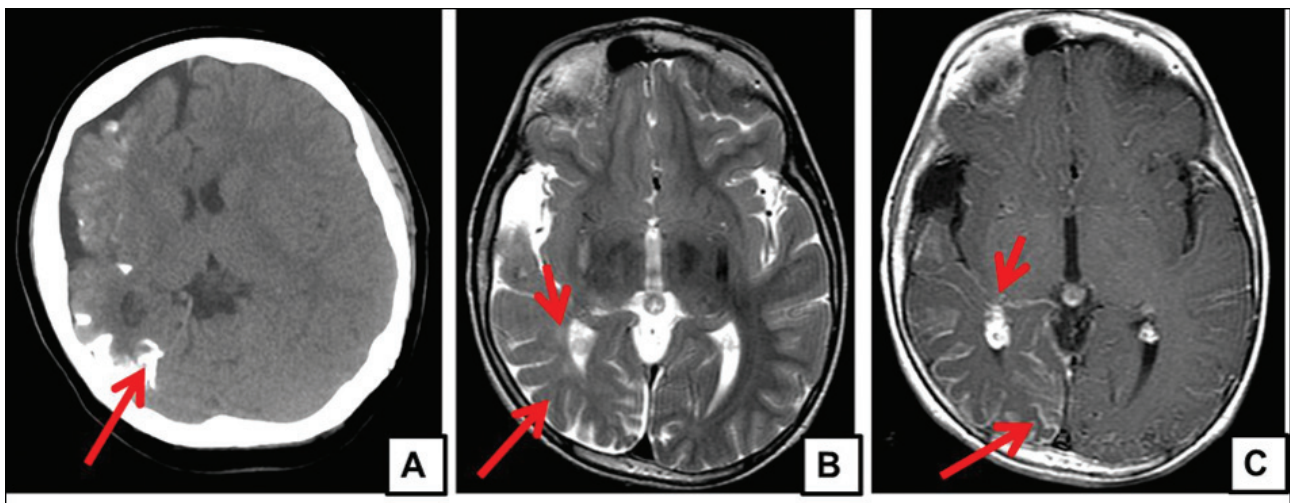


Figure 3 - Brain cranial computed tomography (CT), nonenhanced axial view (A): showing atrophy at the right cerebral hemisphere with right side dense gyriform calcification (arrow) consistent with Sturge - Weber syndrome. Brain magnetic resonance imaging (MRI), axial T2WI (B): showing asymmetry of both hemispheres, right being small in size with brain atrophy and dilated supratentorial ventricular system (left>right), thick cortex (arrow) with reduced right white matter bulk posteriorly (arrow head). Axial post contrast T1WI (C): showing enhancement of the surface of the right cerebral cortex representing leptomeningeal angioma (arrow) with enlarged enhanced ipsilateral choroid plexus in trigone of right lateral ventricle.

DISCUSSION

The patient in this report presented with a clinical overlap between the SW and KTS syndromes. Klippel- Trenaunay Syndrome is a rare mesodermal phakomatosis. Its clinical features include a triad of irregular and asymmetrical capillary port-wine stain and cavernous hemangioma on the trunk or limbs, venous varicosities, and asymmetrical hypertrophy of bone or soft tissue [6]. Other associated clinical features include vascular malformations i.e. arteriovenous fistulae or aneurysms, lymphedema, and visceromegaly [7]. The diagnosis of KTS can be made when any two of the triad features is present. It is usually unilateral and almost exclusively involves lower extremities, buttocks, abdomen and lower trunk. It is rarely bilateral and involves upper extremities. The varicosities appear mostly by age of 12 years [8]. Oduber et al expanded the definition to cover more anatomic variations, so that the vascular malformations and disturbed growth (hypertrophy or hypotrophy) coexist on the same or opposite sides involving part of a limb, a whole limb, a hemibody or a limb girdle [9]. Hypertrophy of soft tissues may be prominent in small body parts such as toes (macroductyly). Capillary malformations (port-wine stains) and venous malformations are both considered as major diagnostic features, whereas small congenital lymphatic malformations simply support the diagnosis of KTS. Limb dystrophic disorders, which are nonessential but still support the diagnosis of KTS, include polydactyly, syndactyly and clinodactyly. Complications that also support the diagnosis include thrombosis, thrombophlebitis, emboli, cellulitis, edema, hemorrhage from the involved epithelia and autonomic dysfunction as evidenced by skin atrophy or hyperhidrosis. Abnormal development (dysplasia) of the venous system involves mostly the deep veins of the lower limbs with vascular defects, phlebectasia and hypoplasia. The common superficial venous system anomalies in KTS are

the persistence of the embryonic lateral marginal vein and varicose veins. The associated central nervous system abnormalities include microcephaly, macrocephaly, hemimegaencephaly, cerebral and spinal arteriovenous malformations or multiple aneurysms and orbito-frontal varices [8,10].

Sturge-Weber syndrome, another mesodermal phakomatosis also called encephalofacial or encephalotrigeminal angiomas, is characterized by purple-colored flat cutaneous facial hemangiomas most commonly along the trigeminal nerve, vascular lesions (angiomas) in the ipsilateral brain, meninges, and choroid plexuses. Neurological dysfunction results from secondary effects of cerebral angioma on surrounding tissue, including hypoxia, ischemia, venous occlusion “vascular steal phenomenon”, thrombosis, infarction and vasomotor phenomenon. Its major clinical features include glaucoma, buphthalmos, macrocephaly, seizures, hemiparesis and neurodevelopmental delay with altered behavior [11,12]. About 70% of patients with epilepsy develop their first seizure within the first year of their life, which results from cortical irritability caused by angioma through the mechanism of hypoxia, ischemia and gliosis; and the majority have focal seizures involving the contralateral side of the port wine stain. Intractability of seizure is well known and the final resolution is surgical intervention. Hemiparesis occurs in 25-56% of patients because of repeated transient ischemic attacks (vascular origin) or postictal event. Cranial CT will show the characteristic the gyriform “tram track” calcification of underlying angioma. Calcification is unusual before 2 years of age, usually involves high parietal or occipital lobes. The “gold standard” for diagnosis is MRI which shows thickened cortex, decreased convolutions, abnormal white matter and gadolinium enhancement of leptomeningeal angioma.

The patient in this report had macrocephaly, port-wine stain, glaucoma, seizures, developmental delay,

left - sided hemiparesis in addition to the classical leptomenigeal enhancement, signs of cortical atrophy, enlarged choroid plexus, and calcification in the adjacent area. All are diagnostic for SWS, while extensive cutaneous vascular lesions and right sided hypertrophy represented the association with Klippel - Treunaunay syndrome [13].

Both syndromes are rare, and the pathogenesis is still not clearly elucidated [11]. In some cases, an association of SW with KTW syndrome seems to exist or there is a clinical and biological overlap between the two diseases. There is even a suggestion that SWS and KTS are the same disease with different manifestations, but it should be considered as separate entities. Both syndromes occur usually sporadically, but a dominant autosomal inheritance has already been described in some families [14]. Recent data suggest that SWS is due to somatic mosaic mutations in the GNAQ gene [15]; while some cases of KTS result from mutation in an angiogenic factor, VG5Q gene that is well known to be involved in early embryonic angiogenesis. There are suggestions that the majority of cases result from somatic mutations involving genes that play significant roles in embryonic vasculogenesis and angiogenesis [16,17].

The overlapping between SWS and KTS is recognized, and over 40 cases of combined SWS and KTS clinical features have been described in the literature [13,18]. The major CT scan abnormalities detected in them were malformation of the circle of Willis, cerebral hemihypertrophy, aplasia of the cervical internal, carotid artery, cerebral atrophy, prominent choroid plexus, cerebral calcifications and leptomenigeal enhancement [2,8,13,18]. Both syndromes are also considered as risk factors for stroke in children and adults [8,19,20]. A few cases of intracranial hemorrhage, and subdural hematoma have been reported in patients with Sturge-Weber syndrome, and it is of interest that this patient needed subdural peritoneal shunt because of left frontal

subdural fluid collection likely to be due to previous subdural hematoma. No clear history of minor trauma as a preceding event, and the patient was off Aspirin therapy.

In general, treatment should be directed to the associated manifestation and detected anomalies. Treatment in SWS includes seizures control, with surgical resection being restricted to refractory cases, close monitoring for glaucoma, and prompt treatment for elevated intraocular pressure, which may include medical as well as surgical decompression, as well as intense rehabilitation for motor paresis. Aspirin prophylaxis reduces stroke-like events (hemiparetic episodes of vascular origin) and seizure episodes and thus can halt the overall neurological deterioration. In KTS, surgical intervention may be needed in the presence of excessive leg length discrepancy, symptomatic varicosities, and localized superficial venous malformations in selected patients. The best treatment for venous thromboembolism (VTE) is the use of low molecular weight heparin with elastic compression stocking as Coumadin (warfarin) therapy alone reportedly fails to prevent recurrence of VTE. Invasive adjunctive therapy with cava filter may be needed with failure of medical therapy or if there is an extension of the venous anomaly to the vena cava.

CONCLUSION

Patients with coexistence of Sturge -Weber and Klippel -Treunaunay syndromes should have timely diagnosis and early surveillance for the associated deep venous malformations. They also require long-term follow up to monitor, control and treat the associated ocular, skeletal, vascular and neurological manifestations to avoid the life threatening complications.

ACKNOWLEDGEMENT

This work was supported by the College of Medicine Research Center, Deanship of Scientific Research, King Saud University.

REFERENCES

1. Comi AM. Presentation, diagnosis, pathophysiology, and treatment of the neurological features of Sturge - Weber syndrome. *Neurologist* 2011;17:179-184.
2. Rahman M, Rahman S, Rahman M, Akhter S, Kawser C. Overlapping of Sturge Weber syndrome and Klippel Trenaunay Weber syndrome. *Mymensingh Med J.* 2008;17:78-81.
3. Cohen MM Jr. Vascular update: morphogenesis, tumors, malformations and molecular dimensions. *Am J Med Genet.* 2006; 140 (19):2013–2038.
4. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge–Weber syndrome: a review. *PediatrNeurol* 2004; 30:303–310.
5. Klippel M, Trenaunay P. Du naevus variqueux ostéohypertrophique. *Arch Gen Med* 1900; 3:641-672.
6. Samimi M, Lorette G. Klippel - Trenaunay syndrome *Press Med.* 2010;39:487-494.
7. Kihiczak GG, Meine JG, Schwartz RA, Janniger CK. Klippel-Trenaunay syndrome: A multisystem disorder possibly resulting from a pathogenic gene for vascular and tissue overgrowth. *Int J Dermatol.* 2006;45:883–890.
8. Verhelst H, Van Coster R. Neuroradiologic findings in a young patient characteristics of Sturge-Weber syndrome and Klippel-Trenaunay syndrome. *J Child Neurol.* 2005;20:911-913.
9. Oduber CE, van der Horst CM, Hennekam RC. Klippel – Trenaunay syndrome : diagnostic criteria and hypothesis on etiology. *Ann Plast Surg* 2008;60(2):217-223.
10. Kiley MA, Oxbury JM, Coley SC. Intracranial hypertension in Sturge-Weber/Klippel-Trenaunay-weber overlap syndrome due to impairment of cerebral venous outflow. *J Clin Neurosci.* 2002;9:330-333.
11. Garzon MC, Huang JT, Enjolras O, Frieden IJ. Vascular malformations Part II: Associated syndromes. *J Am Acad Dermatol.* 2007;56:541–564.
12. Di Rocco C, Tamburrini G. Sturge-Weber syndrome. *Childs Nerv Syst.* 2006;22:909–921.
13. Vissers W1, Van Steensel M, Steijlen P, Renier W, Van De Kerkhof P, Van Der Vleuten C. Klippel-Trenaunay syndrome and Sturge -Weber syndrome: variation on a theme? *Eur J Dermatol.* 2003;13:238-241.
14. Pereira de Godoy JM, Fett-Conte AC. Dominant inheritance and intra-familial variations in the association of Sturge-Weber and Klippel-Trenaunay-Weber syndromes. *Indian J Hum Genet.* 2010;16:26-27.
15. Shirly MD, Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, et al. Sturge-Weber syndrome and port-wine stain caused by somatic mutation in GNAQ. *N Engl J Med .* 2013; 368:1971-1979.
16. Timur AA, Driscoll DJ, Wang Q. Biomedicine and diseases: The Klippel-Trenaunay syndrome, vascular anomalies and vascular morphogenesis. *Cell Mol Life Sci.* 2005;62:1434–1447.
17. Tian XL, Kadaba R, You SA, Liu M, Timur AA, Yang L, et al. Identification of an angiogenic factor that when mutated causes susceptibility to Klippel-Trenaunay syndrome. *Nature.* 2004;427:640–645.
18. Chhajed M, Pandit S, Dhawan N, Jain A. Klippel – Trenaunay and Sturge – Weber overlap syndrome with phakomatosis pigmentovascularis . *J Pediatr Neurosci.* 2010; 5:138–140.
19. Salih MA, Murshid WR, Zahraa JN, Abdel-Gader AG, Al-Jarallah AA, Kentab AY, et al. Congenital and genetic cerebrovascular anomalies as risk factors for stroke in Saudi children. *Saudi Med J.* 2006; 27(1): S53-S60.
20. Ndzengue A, Rafal RB, Balmir S, Rai DB, Jaffe EA. Klippel – Trenaunay syndrome: An often overlooked risk factor for venous thromboembolic disease. *Int J Angiol.* 2012;21:233-236.