

Klippel-Trenaunay-Weber Syndrome with Hemimegalencephaly; Report of a Pediatric Case

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Abstract

Background: Klippel-Trenaunay-Weber Syndrome (KTWS) is a rare neurocutaneous syndrome. Hemimegalencephaly (HME) and seizure episodes have been reported previously in a few cases with KTWS.

Case Presentation: We report here a 3 day-old girl with partial motor seizures, extensive port-wine staining and mild structural deformities in the feet, and a hemimegalencephaly.

Conclusion: Occurrence of partial motor seizures in addition to bilateral lower extremities extensive port-wine staining is a unique feature seen in our case.

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Key Words: Klippel-Trenaunay-Weber Syndrome; Hemimegalencephaly; Neurocutaneous Syndrome

Introduction

Klippel-Trenaunay-Weber Syndrome (KTWS), first described in 1900 by Klippel and Trenaunay^[1], is a rare neurocutaneous syndrome; it comprises a triad of port-wine stain, varicose veins, and hypertrophy of the bones and overlying soft tissue^[2]. Hemimegalencephaly (HME) and seizure episodes have been reported previously in a few cases with KTWS^[3,4]. Here we report a case of KTWS with HME in a newborn infant.

Case Presentation

A 3 day-old newborn girl was brought to our center because of poor feeding along with episodes of a generalized myoclonic activity in extremities, cyanosis and upward gaze. The attacks were repeated 4-5 times a day and lasted for 2-3 minutes each time.

Our patient was the first child of non-consanguineous parents. She was born near term (37-38 weeks) for mother's early spotting. Natural vaginal delivery was the birth route, with Apgar

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score of 9/10. She had normal birth weight (3200 grams).

An increased vertical length of the right ear compared to the left one, with a normal head circumference was present; and an extensive port-wine staining was seen on her feet up to the waist. The foot deformities were seen as wide foot, and wide cleft between fingers in both lower extremities (Fig. 1).

There was a non-pitting edema with normal arterial pulses in both feet. Investigations for metabolic concerns were negative. Brain MRI revealed a hemimegalencephaly and a germinal matrix hemorrhage at the right cerebellum (Fig 2). Cervical arteries and those of the lower limbs were of normal flow in color Doppler ultrasonography. The diagnosis of Klippel-Trenaunay-Weber Syndrome was established based on these findings.

Anticonvulsant therapy with oral Phenobarbital 15 mg daily controlled primarily the seizure attacks. However, the attacks relapsed again about 3 weeks later with this regimen. Oral phenytoin drops with the dose of 15 mg twice daily was added to the treatment protocol. The patient was seizure-free with this combination during about one month of follow up.

Klippel-Trenaunay syndrome is characterized by a triad of port-wine stain, varicose veins, and



Fig 1: Extensive port-wine staining of the lower extremities; note the widened interphalangeal cleft especially in the right foot

bony and soft tissue hypertrophy involving an extremity. The exact cause of KTWS remains to be elucidated, although several theories exist. Bliznak and Staple suggested intrauterine damage to the sympathetic ganglia or intermediolateral tract leading to dilated microscopic arteriovenous anastomoses as the cause^[5]. Servelle believes that

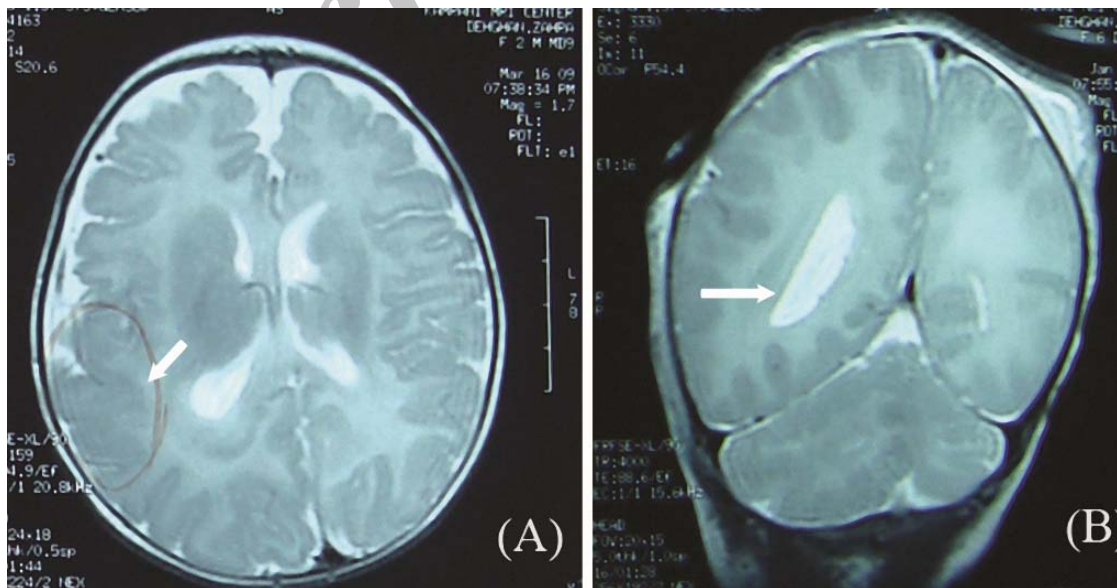


Fig. 2: Right-sided hemimegalencephaly is evident in the T2-weighted brain MRI; note the gyral thickening (arrow, A) and the lateral ventricular widening (arrow, B) in the right cerebral hemisphere.

deep vein abnormalities with resultant obstruction of venous flow lead to venous hypertension, the development of varices, and limb hypertrophy^[6]. Baskerville et al contend that a mesodermal defect during fetal development causes maintenance of microscopic arteriovenous communications^[7]. Finally, McGrory and Amadio believe that an underlying mixed mesodermal and ectodermal dysplasia is likely responsible for the development of KTWS^[8].

Most cases are sporadic, although a few cases in the literature are report as an autosomal dominant pattern of inheritance^[9]. A case report of KTWS in a monozygotic twin with an unaffected twin advances the theory of a paradominant inheritance pattern^[10]. This theory suggests that KTWS is produced by a single gene defect lethal in individuals who are homozygous for this gene. Heterozygotes carry the gene but are unaffected. The disease manifests in individuals who demonstrate loss of heterozygosity from a somatic mutation during embryogenesis. In these individuals, only the skin region harboring this cell population demonstrates the KTWS mutation.

Hemimegalencephaly is a rare but unique malformation characterized by enlargement of all or parts of a cerebral hemisphere. The affected hemisphere may have focal or diffuse neuronal migration defects, with areas of polymicrogyria, pachygyria, and heterotopias^[11]. MR imaging is the imaging technique of choice for diagnosis of this condition. HME was first described by Sims in 1835 after reviewing 253 autopsies^[12]. Although the cause is unknown, it is postulated that it occurs due to insults during the second trimester of pregnancy, or as early as the 3rd week of gestation, as a genetically programmed developmental disorder related to cellular lineage and establishment of symmetry^[13]. HME may also be considered a primary disorder of proliferation wherein the neurons that are unable to form synaptic connections are not eliminated and are thus accumulated. Syndromic hemimegalencephaly is a type that associates with other diseases and may occur as HME of part or all of the ipsilateral body. Males and females are equally affected. However, almost all cases of KTWS already reported with HME were females. Table 1 summarizes the case reports already published in

the literature regarding their sex, age, main problem and associated signs and symptoms.

Discussion

Klippel-Trenaunay syndrome is characterized by a triad of port-wine stain, varicose veins, and bony and soft tissue hypertrophy involving an extremity. The exact cause of KTWS remains to be elucidated, although several theories exist. Bliznak and Staple suggested intrauterine damage to the sympathetic ganglia or intermediolateral tract leading to dilated microscopic arteriovenous anastomoses as the cause^[5]. Servalle believes that deep vein abnormalities, with resultant obstruction of venous flow, lead to venous hypertension, the development of varices, and limb hypertrophy^[6]. Baskerville et al contend that a mesodermal defect during fetal development causes maintenance of microscopic arteriovenous communications^[7]. Finally, McGrory and Amadio believe that an underlying mixed mesodermal and ectodermal dysplasia is likely responsible for the development of KTWS^[8].

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Table 1: Published case reports of KTWS with HME since 1983 in the literature

Author	Publication year	Presentation	Associations	Patient
Vurucu, et al ^[14]	2009	intractable seizures	retroperitoneal lymphangioma and double inferior vena cava	6-year-old girl
Ahmed, et al ^[3]	2008	partial motor seizures	heterotopia on MRI of the brain	13-year-old girl
Obradovic, et al ^[15]	2005	characteristic vascular nevi on the skin	hypertrophy of the left part of the body, temporal hemangioma	newborn boy
Dhamecha, et al ^[4]	2001	developmental delay and seizures	calvarial hypertrophy, but no evidence of limb or trunk hypertrophy	19-year-old girl
Thong, et al ^[16]	1999	psychomotor retardation	hemihypertrophy, macrocephaly, vascular lesions, and intestinal lymphangiectasia	
Alpay ^[17]	1996	congenital hemihypertrophy	nevus flammeus and liver hemangioma	2.5-year-old girl
Chen, et al ^[18]	1996	facial port-wine stain	cutaneous telangiectasia, left facial hemihypertrophy, left facial hemihypertrophy and ipsilateral ventriculomegaly	full-term female neonate
Cristaldi, et al ^[19]	1995	hemihypertrophy	vascular lesions in one of the cases	two 1-month-old children
Burke, et al ^[20]	1991	limb and facial hemihypertrophy	congenital nystagmus, progressive ipsilateral anisomyopia, strabismus	
Cheruy, et al ^[21]	1987	lower limb inequality	dizziness, tinnitus and nystagmus, total hemihypertrophy	female patient
Matsubara, et al ^[22]	1983	right hemihypertrophy	vascular nevus of the right side of the body, multiple haemangiomas, varicosis and chronic proliferative glomerulonephritis	17-year-old Japanese girl

1835 after reviewing 253 autopsies^[12]. Although the cause is unknown, it is postulated that it occurs due to insults during the second trimester of pregnancy, or as early as the 3rd week of gestation, as a genetically programmed developmental disorder related to cellular lineage and establishment of symmetry^[13]. HME may also be considered a primary disorder of proliferation wherein the neurons that are unable to form synaptic connections are not eliminated and are thus accumulated. Syndromic hemimegalencephaly is a type that associates with other diseases and may occur as HME of part or all of the ipsilateral body. Males and females are equally affected. However, almost all cases of KTWS already reported with HME were female. Table 1 summarizes the case reports already published in the literature regarding their sex, age, main problem and associated signs and symptoms. The unilateral hypertrophy and seizures have been the most common associated symptoms in these cases. However, some unusual cases of central

deformities such as double inferior vena cava were seen recently^[14].

Conclusion

Occurrence of partial motor seizures in addition to extensive port-wine staining of both lower extremities is a unique feature seen in our case. Our case was also a female neonate similar to the most of previously published cases. This may take our attention to a sex-dominant genetic or mitochondrial transmission of the disease.

References

1. Klippel M, Trenaunay P. Du naevus variqueux osteohypertrophique. *Arch Gen Med (Paris)* 1900; 3:641-72. (In French)

2. Meine JG, Schwartz RA. Klippel-Trenaunay-Weber syndrome. *Pediatr Dermatol* 1997; 60(3):127-32.
3. Ahmed S, Koul R, Wailey A, Sankhala D. Klippel-Trenaunay-Weber syndrome with partial motor seizures and hemimegalencephaly. *Neurosciences* 2008;13(1):77-8.
4. Dhamecha RD, Edwards-Brown MK. Klippel-Trenaunay-Weber syndrome with hemimegalencephaly. *J Craniofac Surg* 2001;12(2):194-6.
5. Bliznak J, Staple TW. Radiology of angiodyplasias of the limb. *Radiology* 1974; 110(1):35-44.
6. Servelle M. Klippel and Trenaunay's syndrome. 768 operated cases. *Ann Surg Mar* 1985;201(3): 365-73.
7. Baskerville PA, Ackroyd JS, Browse NL. The etiology of the Klippel-Trenaunay syndrome. *Ann Surg* 1985;202(5):624-7.
8. McGrory BJ, Amadio PC. Klippel-Trenaunay syndrome: orthopaedic considerations. *Orthop Rev* 1993;22(1):41-50.
9. Ceballos-Quintal JM, Pinto-Escalante D, Castillo-Zapata I. A new case of Klippel-Trenaunay-Weber (KTW) syndrome: evidence of autosomal dominant inheritance. *Am J Med Genet* 1996; 63(3):426-7.
10. Hofer T, Frank J, Itin PH. Klippel-Trenaunay syndrome in a monozygotic male twin: supportive evidence for the concept of paradominant inheritance. *Eur J Dermatol* 2005; 15(5):341-3.
11. D'Agostino MD, Bastos A, Piras C, et al. Posterior quadrantic dysplasia or hemi-hemimegalencephaly: a characteristic brain malformation. *Neurology* 2004;62(12):2214-20.
12. Sims J. On hypertrophy and atrophy of the brain. *Med Quir Trans* 1835; 19:315-80.
13. Flores-Sarnat L. Hemimegalencephaly. Part I. Genetic, clinical, and imaging aspects. *J Child Neurol* 2002;17(5):373-84.
14. Vurucu S, Battal B, Kocaoglu M, Akin R. Klippel-Trenaunay syndrome with hemimegalencephaly, retroperitoneal lymphangioma and double inferior vena cava. *Br J Radiol* 2009;82(977): e102-4.
15. Obradovic S, Vuletic B, Stojkovic-Andelkovic A, et al. Report of a newborn with hemimegalencephaly in association with Klippel-Trenaunay-Weber syndrome *Srp Arh Celok Lek* 2005;133(1-2):62-4. (in Serbian)
16. Thong MK, Thompson E, Keenan R. A child with hemimegalencephaly, hemihypertrophy, macrocephaly, cutaneous vascular malformation, psychomotor retardation and intestinal lymphangiectasia -- a diagnostic dilemma. *Clin Dysmorphol* 1999;8(4):283-6.
17. Alpay F, Kurekci AE, Gunesli S, Gokcay E. Klippel-Trenaunay-Weber syndrome with hemimegalencephaly. Report of a case. *Turk J Pediatr* 1996; 38(2):277-80.
18. Chen PC, Shu WC. Klippel-Trenaunay-Weber syndrome with hemimegalencephaly: report of one case. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1996;37(2):138-41.
19. Cristaldi A, Vigevano F, Antoniazzi G, et al. Hemimegalencephaly, hemihypertrophy and vascular lesions. *Eur J Pediatr* 1995;154(2):134-7.
20. Burke JP, West NF, Strachan IM. Congenital nystagmus, anisomyopia, and hemimegalencephaly in the Klippel-Trenaunay-Weber syndrome. *J Pediatr Ophthalmol Strabismus* 1991; 28(1):41-4.
21. Cheruy M, Heller FR. An unusual variant of Klippel-Trenaunay syndrome. Association of total hemihypertrophy, hemimegalencephaly and bilateral extremity enlargement (case report). *Acta Chir Belg* 1987;87(2):73-6.
22. Matsubara O, Tanaka M, Ida T, et al. Hemimegalencephaly with hemihypertrophy (Klippel-Trenaunay-Weber syndrome). *Virchows Arch A Pathol Anat Histopathol* 1983;400(2):155-62.