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Evaluation and Management of Pain in Patients with Klippel-Trenaunay Syndrome: A Review

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ABSTRACT. Klippel-Trenaunay syndrome (KTS) is a rare disorder that consists of a triad of capillary vascular malformation, venous malformations and/or varicose veins, and soft tissue and/or bony hypertrophy. Pain is a real and debilitating problem in these patients. We have observed 9 common causes of pain in KTS: (1) chronic venous insufficiency, (2) cellulitis, (3) superficial thrombophlebitis, (4) deep vein thrombosis, (5) calcification of vascular malformations, (6) growing pains, (7) intraosseous vascular malformation, (8) arthritis, and (9) neuropathic pain. The management of pain in patients with KTS depends on its cause. These patients are best evaluated initially in a center with an experienced multidisciplinary team that includes a primary health care provider, surgeons, and ancillary staff. The ongoing care of a patient with KTS often depends on a local provider who is more readily accessible to the patient but may not have the expertise of a large center to manage the complications of KTS. The purpose of this communication is to review the common causes of pain in these patients to provide local health care providers and patients and their families with appropriate management strategies. *Pediatrics* 2005;115:744-749; pain, pain management, Klippel-Trenaunay syndrome, vascular malformation, chronic venous insufficiency.

ABBREVIATIONS. KTS, Klippel-Trenaunay syndrome; DVT, deep vein thrombosis.

Klippel-Trenaunay syndrome (KTS) is a rare disorder that comprises the triad of (1) capillary vascular malformation, (2) varicose veins and/or venous malformation, and (3) soft tissue and/or bony hypertrophy.¹⁻⁴ It is a mixed malformation with soft tissue and bony malformations and is associated with predominantly venous, lymphatic, and capillary vascular malformations, with involvement of usually 1 of the lower limbs. Chronic lymphedema will frequently aggravate the clinical presentation. The manifestations of KTS are protean, and, in many patients, pain is a frequent and debil-

itating problem. We previously⁵ reported that 38% of patients had significant pain, and Baskerville et al⁶ found that 88% of their patients had pain. The lower extremity is most often affected in KTS, and pain is a great problem in these patients compared with those whose upper extremity is affected.

Over the past 25 years, we have collectively had the opportunity to evaluate and treat >300 patients with KTS.^{5,7-13} On the basis of this experience, we have observed several different patterns and causes of pain. It has become clear that to deal appropriately with pain in patients with KTS, one first must define the exact cause of the pain. The purpose of this communication is to share our experiences so that patients with this rare problem receive the best possible care.

THE MAYO MODEL OF CARE FOR VASCULAR MALFORMATIONS

At Mayo Clinic Rochester, we use a multidisciplinary approach to the evaluation and treatment of patients of all ages with vascular anomalies, including KTS. The core of this team includes a pediatrician/family physician or internist and vascular, orthopedic, and plastic surgeons. In addition, the expertise of vascular internists of the Gonda Vascular Center, radiologists, physiatrists, pain management specialists, and dermatologists are employed. Periodically, formal reviews of our experience are conducted and published. The basis of this communication is the cumulative experience of this multidisciplinary team.

CAUSE OF PAIN IN KTS

We believe that there are 9 common causes of pain in KTS. Some patients may have only 1 cause of pain, but others may have several causes of pain.

Chronic Venous Insufficiency

Venous abnormalities are a hallmark of KTS. Superficial varicosities; persistent large superficial embryonic veins, usually in the lateral position in the leg; and deep venous valvular incompetence, aneurysmal dilation, hypoplasia, or aplasia are common. Varicose veins become more prominent and problematic with increasing age. Ambulatory venous hypertension is a well-defined entity because of increasing venous pressure after exercise as a result of valve incompetence or outflow obstruction. The discomfort that results from generalized venous conges-

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tion is poorly understood, but clearly, varicosities and venous malformations are more painful when distended with venous blood. The discomfort associated with venous incompetence is usually described as a "dull, achy" sensation and typically is more noticeable as the day progresses because of venous pooling of blood.

Varicose veins have been thought to result from primary valvular incompetence. Recent theories propose that decreased elasticity of vein walls cause dilation of the walls, leading to separation of the valve leaflets.¹⁴ Others have shown that varicosities can result even without valvular incompetence.¹⁵ Persistence of embryonic veins that normally regress during gestation is clearly a major cause of varicosities in KTS. Another plausible explanation that has been proposed for increased venous congestion is inefficient calf pump function. However, Baskerville et al⁶ compared foot volumetry in normal patients and KTS patients and found no significant differences in reduction of foot volumes during exercise to suggest inefficient calf pump in limbs of patients with KTS.

Chronic venous congestion can lead to pigmentation, eczema, lipodermatosclerosis, varicosity, atrophy blanche, corona phlebectatica, and, ultimately, breakdown of the skin and ulcerations. It has been found that the severity of the skin ulceration correlates with the degree of ambulatory venous hypertension.^{16,17} Patients with ambulatory venous pressure <40 mm Hg had a lower incidence of skin ulcers than patients with ambulatory venous pressure >80 mm Hg.¹⁸

The mainstay of treatment of this type of pain and discomfort is external compression of the venous system. It can be treated with elastic or nonelastic compression garments. It usually is best to use a closed-toe compression garment. The length of the garment is dictated by the extent of leg involvement. However, we have found that if the entire leg is involved, then a full-length pantyhose-type garment works best. This type of garment is least likely to drift downward while worn and also can provide compression to the groin and buttocks. The greatest pressure that the patient can tolerate should be used. Most patients can tolerate compression of 40 to 50 mm Hg. However, some patients cannot tolerate this level of pressure and will need compression of 30 mm Hg. Foot and leg overgrowth can present a challenge to fitting appropriately a support garment and a challenge to the patient to put on the garment. In some patients, it will be impossible to design a garment that can be applied because of a very large foot. These patients will have to be instructed in methods of wrapping the extremity with compression bandages. In rare cases of complete deep vein obstruction, patients with large superficial veins do not tolerate compression garments. Duplex evaluation of the venous anatomy in these patients is very important.

Frequent elevation of the extremity during the day is very important in reducing pain and the development of stasis ulcers. At all times, when it is possible to elevate the affected extremity, it should be done.

We frequently recommend elevating the foot of the bed for good drainage of the venous system during the night. In severe cases, a patient may have to alter his or her occupation from a job that requires prolonged standing to one that allows the patient to sit and, preferably, elevate the leg.

In selected cases, surgical intervention, sclerotherapy, or endovascular laser ablation may be indicated in patients who are symptomatic with pain and edema. Asymptomatic patients are usually managed conservatively because of the high (50%) recurrence rate of varicosities.⁹ In the highly selected group of patients who are considered for surgical procedures, a thorough assessment of the venous anatomy should be performed with duplex scanning, contrast phlebography, MRI, and magnetic resonance phlebography. Duplex scanning and ascending and descending phlebography are used to assess valvular incompetence of the deep, superficial, or perforator veins; discover deep venous anomalies and obstructions; and assess collateralization, respectively. Frequently, the abnormalities seen in KTS include persistence of embryonic veins, agenesis, hypoplasia, valvular incompetence, or aneurysms of deep veins.

The most common surgical treatment in patients with KTS is stripping of the veins and avulsion or excision of varicosities and vascular malformations. The primary goal of imaging is to confirm patency of the deep venous system before these procedures are performed. In a very rare subset of patients, removal of the tortuous but patent superficial venous system leads to venous hypertension if deep venous reconstruction is not also performed. Although most surgical procedures for varicosities are uncomplicated, it is often impossible to remove all varicosities because of the extent of involvement. Fifty percent of patients who have surgery will have some form of recurrent varicosities. Despite this, patients report subjective improvement in symptoms and an overall clinical improvement as reflected by a reduction in the clinical severity score after surgery.⁹ Recurrent varicosities can and have been reoperated on if the benefits outweigh the risks of the procedure. Sclerotherapy of cavernous venous malformation with alcohol and foam sclerotherapy of the venous malformations have been used by others, with mixed results.

Cellulitis

Patients with KTS are prone to cellulitis, and whether this is attributable to an actual bacterial infection or an inflammatory response as a result of venous stasis, localized lymph accumulation, or thrombosis is not always clear.¹⁹ Chronic lymphedema is clearly a major cause of cellulitis and lymphangitis. In our series,⁵ 13% of patients had infectious cellulitis. These patients may be more susceptible to infection because of poor skin integrity or from venous pooling. Thus, it is imperative for patients to maintain excellent skin hygiene. Maintaining strict hygiene can be challenging because of hyperhidrosis associated with KTS that is accentuated by the use of stockings, shoes, etc. Particularly for patients with significant foot and toe involve-

ment, thorough washing of leg, foot, and toes may be challenging. We encourage patients to wash the affected body parts thoroughly with soap and water twice a day. If the patient prefers showers to bathtubs, then we suggest that he or she place a stool in the shower so that he or she can sit and wash thoroughly between the toes. It is imperative that patients wear clean stockings every day and allow their shoes and feet to dry between shoe changes. These patients should avoid going barefoot.

For some patients, use of a compression garment will reduce the incidence of cellulitis, but in others, it may increase the risk for cellulitis because of the associated hyperhidrosis or because of abrasions of keratohemangiomas by the stocking. One must experiment with this to know which is best for individual patients.

If there is new-onset erythema, local discomfort, and warmth, then cellulitis always must be suspected. It is imperative to treat these patients with antibiotics as soon as the diagnosis is apparent.

Usually, patients who have had recurrent cellulitis are able to recognize the heralding symptoms of cellulitis up to 24 hours before the infection is clinically apparent. For these patients, we suggest that they have a 10-day supply of an appropriate antibiotic at home so that they can begin taking antibiotics at the first sign or symptom of cellulitis. In rare patients, this may not be enough to prevent serious recurrent cellulitis, and one must consider prophylactic antibiotics. We think that it is best in these situations to consult with an infectious disease expert to plan the most appropriate course of treatment for these rare situations.

Growing Pains

Growing pains are normal in healthy children. Children with KTS are just as likely to have growing pains as are healthy children. The muscles are affected more so than the joints, and the area is usually normal on examination with no evidence of erythema, skin ulceration, mass, or swelling. Compared with pain caused by other factors, that of growing pains is relieved by simple comforting measures such as holding, stroking, and massaging of the limb.

Thrombophlebitis

Inflammation of the superficial veins is common in KTS and, in our series,⁵ occurred in 15% of patients. Aseptic inflammation probably results from venous stagnation in the lower extremity varicose veins. This type of pain is best treated with simple analgesics and antiinflammatory agents along with compression and elevation. If recurrent, then vein stripping, ligation, or injection sclerotherapy may be helpful. This should be undertaken only in a select group of patients in whom an intact deep venous system has been demonstrated. In patients with large embryonic veins or when the saphenous junctions are involved, anticoagulation should be considered.

When left untreated, superficial thromboses usually are a self-limiting problem. In 7 to 14 days, the pain subsides and a small knot may be palpable (the organized thrombus). These clots may calcify and

become “phleboliths” that are apparent on radiographs. Treatment, if used, consists of nonsteroidal antiinflammatory agents and mild analgesics.

When a calcified phlebolith is on a weight-bearing surface (Fig 1), such as the plantar aspect of the foot, it can be painful when downward pressure is applied on the foot. Adding a pad to the insole will usually relieve this type of pain.

Deep Vein Thrombosis

Deep vein thrombosis (DVT) is more common in patients with KTS than in those with normal varicose veins.²⁰ In our series, 11 (4%) of 252 patients had documented DVT.⁵ It is important to diagnose and treat immediately any DVT with anticoagulation or, selectively, with thrombolytics if the DVT involves the large iliofemoral veins. Pain is a usual presentation, in addition to swelling and cyanotic discoloration of the leg.

We recommend that patients with KTS avoid estrogen-containing contraceptives and heed precautionary measures to prevent thrombosis during long periods of immobilization. Whether patients with KTS should receive prophylactic anticoagulation therapy or antiplatelet therapy is controversial. Certainly prophylactic anticoagulation therapy should be considered for patients who have had recurrent DVTs, particularly when complicated by pulmonary embolus. It is unclear whether prophylactic anticoagulation or antiplatelet therapy is effective in preventing superficial thrombophlebitis. Considering that spontaneous bleeding from superficial venular blebs can be problematic, one must consider this when contemplating chronic anticoagulation. Patients with recurrent DVT should be considered for placement of an inferior vena cava filter to prevent major pulmonary embolus.



Fig 1. Phlebolith on the plantar aspect of the heel, which resulted in heel pain.

Intraosseous Vascular Malformations

Rarely, patients with KTS can have intraosseous vascular malformations.²¹ Although rare, they usually occur in long bones (Fig 2), but we have reported 1 patient¹³ who had multiple osteolytic lesions of the calvarium (Fig 3). These lesions cause intense pain. When they involve long bones, there is an increased risk for fracture. A variety of analgesics can be tried, but in most cases, surgical removal of the malformation may be necessary. If the lesions cannot be removed, then management of the pain can be challenging. Some of these patients may require long-term opiates for pain control.

Calcified or Scarified Vascular Malformations

Calcified vascular malformations can be a source of pain if located around structures that are mobile, such as the ankle joint (Fig 4). We have seen this occur in natural calcification of a vascular malformation. We have also seen it as a result of sclerotherapy of a vascular malformation. If well localized, then surgical removal may relieve this type of pain.

Arthritis

In a study of 27 patients with purely venous malformations occurring within the extremities, it was found that 81% (13 of 16) of lower limb cases and 36% (4 of 11) of upper limb cases involved arthritis of the knee and elbow joint, respectively. In 7 of the 16 lower limb cases in this study, patients had to undergo surgical treatment for severe functional impairment, which consisted of synovectomy and excision of the venous mass.²² In our experience, arthritis occurs in a very small number of patients with KTS,



Fig 2. Intracavitary vascular malformation of the tibia. The patient had significant pain from this lesion and also had a pathologic fracture.

but in those patients, it is a major problem. Usually it involves the knee, but we have also treated patients with ankle involvement. MRI of the affected joint will establish the presence of intra-articular vascular malformation. Proliferative vascular synovitis and an associated joint effusion is the usual accompanying findings on MRI.

Destruction of cartilage occurs probably from recurrent hemarthrosis when the vascular malformation is within a joint (Fig 5). Alternatively or in addition, the presence of the vascular malformation may create a chronic synovitis. Patients with this have pain and, as a result, keep the knee flexed, and they can develop a flexion contracture.

Treatment includes analgesics and maneuvers to prevent the flexion contracture. This may involve physical therapy, passive stretching, and bracing. Synovectomy may be useful but is unproved at this time. If the flexion contracture is severe enough to prevent walking and the leg cannot be straightened, then amputation may be necessary to control the pain and allow the patient to walk (with a prosthesis).

Neuropathic Pain

Neuropathic pain results from damage or dysfunction of neuronal pathways and is a shooting, burning, aching (or a combination) pain that is poorly responsive to conventional analgesics. It often occurs in areas with altered sensation. We have evaluated 4 patients who have KTS with neuropathic pain. Their pain is disabling and associated with hyperesthesia. All 4 patients are adults, and all have KTS involving the leg. Three of the 4 had extensive surgical procedures on the leg, and in 2 of these, the pain occurred after the surgical procedures. We speculate that neuropathic pain can result from damage to nerves at the time of operation. Also, we think that this pain can result from effects of the venous abnormality on the nerve that shares the neurovascular bundle. It may result from direct compression of the nerve and/or abnormal venous pressure of the nutrient vascular system of the nerve.

The management of neuropathic pain is difficult as such pain responds poorly to conventional analgesics and less well to opioids. In the past 30 years, antidepressants and anticonvulsants have been the 2 major classes of drugs used to treat neuropathic pain.^{23–25} Their mechanism of action relies on inhibition of excitatory pathways or enhancement of inhibitory pathways. Drugs such as carbamazepine, phenytoin, lamotrigine, and felbamate inhibit the excitatory sodium channels, whereas valproic acid increases the inhibitory pathways of γ -aminobutyric acid. In this manner, the excess firing of neuronal pathways that lead to pain is dampened. The choice of which agent to use is a matter of trial and error as not one has been shown to be more efficacious than another. We tend to introduce 1 agent at a time at a low starting dose, titrate up to desired effect, and if not beneficial after a trial period of 2 to 3 weeks, we substitute another agent. More than 1 drug is sometimes necessary to control the pain. The short-term

Fig 3. Vascular malformation of the calvarium. The patient had severe headaches from these lesions.



Fig 4. Calcified vascular malformation of the anterior aspect of the ankle. The patient was active athletically, and this lesion produced significant pain and impairment. It was resected, and the patient did well.

use of steroids (Prednisone) can also be used for acute neuropathic pain.

DISCUSSION

KTS occurs in 1 of 20 000 to 40 000 live births. The manifestations of KTS are protean and historically has been confused with other overgrowth syndromes such as Proteus syndrome and Parkes Weber syndrome. The absence of clinically significant arteriovenous shunting distinguishes KTS from Parkes Weber syndrome.²⁶

The triad of capillary malformations (port wine stain), varicosities or venous malformations, and limb hypertrophy has been found to occur in 98%, 72%, and 67% of patients, respectively, in our series⁵ of 252 patients. All 3 features were present in 63% of patients, and 37% had 2 of the 3 features, which



Fig 5. MRI of the knee demonstrating intra-articular vascular malformation.

illustrates that not all patients with KTS have all 3 features of the triad, and patients can receive a diagnosis of KTS with only 1 or 2 features. The cause of KTS is still unclear. Several theories have been proposed, including (1) Servelle's theory of a primary obstruction of the venous system resulting in venous hypertension and therefore development of abnormal venous pathways and tissue overgrowth; (2) failure of regression of the lateral limb bud vein; and (3) alteration of the tight balance between angiogenesis and vasculogenesis, which is controlled by numerous genes, among other theories.²⁷⁻³⁰ KTS is a mixed malformation whereby soft tissue and bony malformation is associated with predominantly ve-

nous, lymphatic, and capillary vascular malformations, with involvement of usually 1 of the lower limbs.

Although pain is such a prevalent morbidity factor and affects up to 88% of patients with KTS, the causes of pain have not been well documented up until now. We have observed that there are 9 most common causes of pain in these patients: (1) chronic venous insufficiency, (2) cellulitis, (3) thrombophlebitis, (4) DVT, (5) calcification of vascular malformations, (6) growing pains, (7) intraosseous vascular malformation, (8) arthritis, and (9) neuropathic pain. Common complications that accompany KTS and also may contribute to pain include pregnancy-associated complications, coagulation abnormalities, and the psychological effects of the visible overgrowth.

Perhaps chronic venous insufficiency accentuates and predisposes to the other causes of pain. If that is the case, then controlling the venous insufficiency and improving venous drainage might reduce pain of a variety of causes. Although the true pathophysiology of venous insufficiency is not yet fully understood at this point, mechanisms that incorporate external compression, limb elevation, exercise, and even a pump to improve venous drainage may be beneficial.

Because it is such a rare condition and because of its protean manifestations, most health care providers are uncomfortable treating patients with KTS. Hence, most patients become frustrated by their inability to find local health care providers who can help them deal with the many complications associated with KTS. For patients in whom pain significantly affects their quality of life, it is important to have local health care providers who can work with the patients on an ongoing basis to manage chronic pain. Because there are numerous causes of pain in KTS, the first step in management is to define the exact cause of the pain. One also must recognize that individual patients may have >1 source of pain, and treatment strategies must be designated to deal with all of the types of pain in an individual patient. A multidisciplinary team that has experience with KTS may best perform the initial evaluation of these patients. However, a local health care provider is best in providing ongoing care. We hope that this review will be useful to achieve this.

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