Deep venous thrombosis in children and adolescents

MICHAEL L. LEVY, M.D., PH.D., ROBERT C. GRANVILLE, B.S., DAVID HART, M.D., AND HAL MELTZER, M.D.

Department of Neurosurgery, Children’s Specialists of San Diego, and University of California, San Diego; and Department of Neurosurgery, Keck School of Medicine, University of Southern California, Los Angeles, California

Object. The objective of this retrospective review was to identify patients on the pediatric neurosurgical ward with deep venous thrombosis (DVT) to develop diagnostic and treatment-related guidelines.

Methods. The authors performed a retrospective chart review of all cases of DVT presenting to the Children’s Hospital between March 1986 and February 1997. Of 32 patients identified, 14 were followed by the neurosurgical service. Current records were additionally evaluated to assess follow-up condition in the patients as well as outcome. Variables included diagnosis, race, age, follow-up duration, outcome, presenting signs/symptoms, involved vessel(s), concurrent disease, diagnostic modalities, and treatment.

Patient age ranged from 1 to 16 years (mean 12.6 years, median 15 years). There were five girls and nine boys. Eight DVTs were right sided and six were left sided. Presenting symptoms included swelling of the affected extremity in 11 patients, pain in five, erythema in one, and cardiopulmonary arrest in two. Comorbidities included previous orthopedic procedures in three, brain tumors in two, and sepsis, fracture, pulmonary disease, preexisting coagulation disorders, and brain abscess in one patient each. Eight patients presented with a history of trauma. Two patients had undergone chemotherapy. Diagnostic studies included ultrasonography and venography in one, venography alone in two, computerized tomography (CT) scanning and venography in one, tagged red blood cell studies in one, ultrasonography and CT scanning in one, and ultrasonography alone in eight. In one patient an inferior vena cava filter was placed and one patient was treated with oral warfarin alone. One patient with a brain tumor died while hospitalized. In four patients there was evidence of rheumatological disease in the group of patients not treated neurosurgically. Two patients suffered recurrences during the follow-up period (mean 20 months). In the entire series of 32 patients there were five total deaths. Of these, two patients experienced six recurrences each, and one other patient suffered four recurrences. Of note, none of the recurrences was observed in patients with underlying coagulation disorders.

Conclusions. Children with DVT can experience serious complications in the form of both morbidity and mortality. Although most thrombotic complications have been found in patients with femoral lines, prolonged treatment involving a central line has been found to be a significant predictor of DVT. Multiple treatment modalities currently exist for children with DVT. Low-molecular weight heparin therapy has many benefits over unfractionated heparin agents and may be more appropriate for the prophylaxis or treatment of children and adolescents with DVT because of its acceptable safety and efficacy. Clinical data for neonates and young children remain incomplete.

Key Words • deep venous thrombosis • diagnosis • treatment • pediatric neurosurgery

Abbreviations used in this paper: CT = computerized tomography; DVT = deep venous thrombosis; IVC = inferior vena cava; MVA = motor vehicle accident; SCI = spinal cord injury; tPA = tissue plasminogen activator.

The increasing incidence of pediatric DVT (approaching 0.2% in North America) is the result of improved care in children with congenital heart disease, prematurity, and cancer. A more significant contributor is the increased use of central venous lines in these children.10 Deep venous thrombosis warrants comprehensive consideration and management because its extension can be realized as fatal pulmonary embolisms. Proper diagnosis and effective prophylactic treatment have been shown to improve associated mortality and morbidity rates. The goal of this study was to evaluate the presentation, management, and outcome in children and adolescents with DVT to determine effective diagnostic and management guidelines.

A current estimate of the incidence of DVT in Canada is 5.3 episodes per 10,000 admissions or 0.07 episodes per 10,000 in the general population.10 In the US, its incidence has been estimated to be 250,000 cases annually.6 Its incidence in children is roughly one tenth that of adults; this disparity may be due to numerous protective mechanisms in children. Risk factors for DVT in adults include malignancy, steroid agent supplementation, major orthopedic surgery (total hip or knee replacement), elective neuro-
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surgery, spinal cord trauma, multiple trauma, pregnancy, puerperium, advanced age, obesity, prolonged immobilization, history of thrombosis, and atrial fibrillation. Unfortunately, risk factors in children have not been well described. Based on the Canadian Registry, the thrombosis-related mortality rate was 2.2% in children, with all deaths occurring in patients in whom central venous lines were present.16

Clinical Material and Methods

Following institutional review board approval, we retrospectively reviewed all patients evaluated for DVT at the Children’s Hospital of Los Angeles between March 1986 and February 1997. Thirty-two cases were identified. Current records were additionally evaluated to assess follow-up condition and outcome. Variables recorded included diagnosis, race, age, follow-up duration, outcome, presenting signs/symptoms, involved vessel(s), concurrent disease, diagnostic modalities, and treatment.

Results

Of 32 children identified with DVT during their hospitalization, 14 were patients followed by the neurosurgical service (Table 1). Age ranged from 1 to 16 years (mean 12.6 years, median 15 years). There were five girls and nine boys. Overall, three patients underwent orthopedic intervention, three harbored brain tumors, and eight presented after trauma (one with active pulmonary disease, one with a preexisting coagulation disorder, and one with a secondary cerebral abscess).

Comorbidities in children admitted with brain tumors included line sepsis in one patient following resection of a posterior fossa tumor and an uncomplicated resection of a posterior fossa tumor in a 3-year-old patient. In one 15-year-old patient with tuberous sclerosis diagnosis was established after an uncomplicated resection of a subependymal giant cell astrocytoma. Two patients received chemotherapy.

Three patients presented after undergoing complex spinal fusion. In one, the course was uncomplicated, in one an associated seizure disorder was present, and paraplegia developed in one secondary to surgery.

In the remaining eight patients DVT resulted after admission to the hospital for trauma. Six patients presented with severe closed head injuries following MVAs: one suffered an associated hemiparesis and developed hydrocephalus, which required the placement of a ventriculoperitoneal shunt; three presented with associated quadripareisis; one presenting with a traumatic intraventricular hemorrhage developed a brain abscess; and one presented with a diffuse right internal carotid artery distribution infarction as well as a tibial fracture. In the remaining two patients, one suffered a penetrating injury of the right sciatic nerve and the one sustained a penetrating frontal lobe injury. In the latter case there was a history of protein S deficiency.

Location of DVTs

In eight patients the DVT was right sided and in six it was left sided. In seven patients two or more vessels were involved: involvement of the IVC in two, the iliac in six, the femoral in six, and the popliteal distribution in three. Of the seven patients with involvement of a single vascular distribution, the femoral vein was involved in all seven patients.

Overall, the IVC was involved in two cases (both with multiple-vessel involvement), the iliac vein in six (all with multiple-vessel involvement), the femoral vein in 13 (46% with multiple-vessel involvement), and the popliteal in three case (all with multiple-vessel involvement). For multiple compared with single vessel involvement, the distribution by side was even: half of the patients with left-sided DVT had multiple-vessel involvement and half with right-sided DVT had multiple-vessel involvement. No bilateral involvement was noted in the series.

Presenting Signs and Symptoms

Presenting symptoms included swelling of the affected extremity in 11 patients, pain of the involved extremity in five, erythema in one, and cardiopulmonary arrest in two. Of the latter two patients, one was a 13 year old in whom arrest occurred after a spinal fusion. This child also had a history of a seizure disorder that was treated with Dilantin. Ultrasonography revealed a clot that diffusely involved the right leg, and treatment was initiated. The other patient was a 6 year old in whom arrest occurred during an admission for a closed head trauma and associated quadriaparesis with severe pulmonary compromise. Both CT scanning and venography were used to diagnose a right-sided DVT. Even in reviewing the presentation data obtained in these two patients, no other findings were evident prior to cardiac arrest. Neither patient underwent placement of an IVC filter for treatment.

Diagnosis and Treatment

Diagnostic studies included ultrasonography and venography in one patient, venography alone in two, CT scanning and venography in one, tagged red blood cell studies in one, ultrasonography and CT scanning in one, and ultrasonography alone in eight. Twelve patients received intravenous heparin therapy followed by oral warfarin. In one patient an IVC filter was placed, and another received oral warfarin alone. One patient with a brain tumor died while hospitalized of sequelae unrelated to the DVT.

Of the 32 patients overall, five patients suffered recurrences. Of these 14 patients two sustained recurrences during the follow-up period (mean 20 months): one suffered six recurrences and the other four recurrences. An underlying coagulation disorder (which can increase the probability of DVT by as much as threefold the norm) was absent in both cases. Specifically, elevated levels of antiphospholipid antibodies, deficiencies of protein C, protein S, plasminogen, and/or antithrombin III were not identified.

Discussion

Incidence of DVT

The overall rate of DVT in adult trauma patients was six per 1000 trauma discharges compared with 0.77 per 1000 in pediatric trauma patients.
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<th>Died</th>
<th>FU (mos)</th>
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Mean ± standard deviation: 12.6 ± 5.1, 23.5 ± 18.9

* Abbreviations: chemo = chemotherapy; CHT = closed head trauma; fem = femoral vein; FU = follow up; ICA = internal carotid artery; IVH = intraventricular hemorrhage; LMWH = low-molecular-weight heparin; pop = popliteal; ultra = ultrasoundography.
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1000 discharges in children younger than 15 years of age. The relative risk of DVT in adults compared with children has been reported at 7.2.\textsuperscript{26} The reported incidence of DVT in adult neurosurgical patients ranges from 19 to 50%,\textsuperscript{12} with DVT being the most frequent complication after craniotomy for tumors.\textsuperscript{9} It has been postulated that this is the result of high levels of cerebral thromboplastin being liberated into the bloodstream. The incidence of DVT in children is increasing (approaching 0.2% in North America) as a result of improved care for heart disease, prematurity, and cancer as well as the increased use of central venous lines.\textsuperscript{18}

**Causes of DVT**

Adult DVT occurs in greater than 50% of patients after stroke and in approximately 50% after major lower-limb orthopedic operations performed without antithrombotic prophylaxis.\textsuperscript{25} Risk factors in adult neurosurgical patients include malignant brain tumors, SCI, plegia, ethnicity, and stroke.\textsuperscript{24} Spasticity may actually play a role in preventing DVT in paralyzed patients, although this does not fully explain the absence of DVT in this population.\textsuperscript{22} Its frequency ranges from 25 to 45% in adults with malignant brain tumors, with tumor type and region being the significant variables.\textsuperscript{12} It has been concluded that suprasellar tumors, meningiomas, and malignant gliomas most effectively promote hypercoagulable state.\textsuperscript{23}

Of a reported 58 recurrent events of venous thromboembolism, 41 occurred in patients with residual thrombosis.\textsuperscript{20} In a series of 885 patients presenting with DVT, 70 were associated with trauma and 22 with neurological disorders. Distal DVT is more frequently associated with bilateral symmetry.\textsuperscript{19} In our series, three patients harbored brain tumors, three underwent spinal stabilization, and seven presented after trauma. Overall, four children were hemiparetic, three were paraparetic, and one was quadriplegic.

Predictive factors for DVT in children with or without embolic disease include neubroblasticoma involving the IVC, positive family history, and a history of thrombotic disorder. These children should be evaluated for DVT and prophylactic anticoagulation therapy considered, especially prior to cytotoxic therapy. In a prospective study of 56 children with DVT, the authors reported prothrombotic disorders in 26 patients (46%; nine with inherited, 13 with acquired, and four with combined disease). Risk factors included factor V G1691A mutation, prothrombin G20210A variant, methyltetrahydrofolate reductase T677T genotype, tPA inhibitor–1 promoter polymorphism, lipoprotein A, antithrombin, protein C, and protein S. The authors concluded that early-onset DVT in children results from combinations of at least two prothrombotic risk factors. Evaluation should be undertaken in children with DVT in whom one or more risk factors are present.\textsuperscript{2}

Deep venous thrombosis has been reported in adults with severe head (Abbreviated Injury Scale score \(\geq 3\)), thoracic, abdominal, lower-extremity, and spinal injuries. No such relationship has been reported for severe upper-extremity injuries. At 6.5 per 1000 discharges, patients with severe spinal injuries were most likely to be affected. When specific injuries were considered, major vascular injury was most strongly associated with DVT with a relative risk of 28.2, as well as pelvic fractures and SCIs with relative risks of 4.4 and 7.9, respectively. Interventions independently associated with DVT in children after traumatic injury include craniotomy, open reduction and internal fixation of lower extremity fractures, laparotomy, and central venous catheter placement.\textsuperscript{26} In children with central venous catheters the relative risk was 39.9 and the absolute rate was 28.6 per 1000 discharges.\textsuperscript{26}

**Diagnostic Testing**

Although venography remains the gold standard, less invasive methods such as ultrasonography and impedance plethysmography are becoming increasingly popular in children.\textsuperscript{18} In our series diagnostic venography was used in four patients in whom DVT was further verified by ultrasonography in one and CT scanning in one. Compression and duplex ultrasonography is the most frequently used diagnostic test in children. It avoids the potential for dye-induced reactions, phlebitis and thrombosis; is easy to perform; and is sensitive to DVT in the lower extremities. Ultrasonography is more sensitive in the femoral and popliteal veins (diagnostic rate \(> 90\%\)) than in the calf veins (diagnostic rate 50%).\textsuperscript{8} Sensitivity is dependent on the experience of the technician.

Although calf vein thrombosis is less frequent, proximal extension can occur in 10 to 20% of distal thromboses, and fatal pulmonary embolism is more common (1–5%).\textsuperscript{25} Serial ultrasonography can reduce the risk of proximal extension or recurrence to less than 2% if two negative tests are obtained within 7 days of each other.\textsuperscript{25}

**Deep Venous Thrombosis–Related Complications**

Complications occur despite prophylactic measures. Short-term complications include edema, pain, and limb discoloration. Long-term complications include recurrence (8.1%) and postthrombotic syndrome (pain, swelling, and ulceration) in 12.4%.\textsuperscript{18} In this series, one patient experienced a recurrent seroma that became infected with pseudomonas; one patient (noncompliant with treatment) suffered a recurrence, and one developed thrombocytoopenia necessitating a change in medical management.

**Initial Management**

Although indications for IVC filter placement include lower-extremity DVT and/or pulmonary embolism, no guidelines exist regarding their use in children.\textsuperscript{13,14,21} In one study of 14 children, investigators documented a safety profile and efficacy in children similar to those seen in adults. There were no instances of pulmonary embolism, IVC thrombosis, significant postphlebitic symptoms, or significant filter migration during the long-term follow-up period.\textsuperscript{3} In our series a filter was used in one patient with DVT involving the left IVC and iliac veins. The child was also treated with low-molecular-weight heparin.

In children tPA therapy is associated with a low margin of safety and an unknown risk/benefit ratio. In one adult study there were major complications in 40% of patients and minor complications in 30%, with cerebral ischemia in two and intracranial hemorrhage in two. Increased complications of tPA therapy are directly related to a decrease in the patient’s weight, longer duration of therapy, decrease in fibrinogen levels, and residual DVT.\textsuperscript{11}

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Four antithrombotic agents are available for treatment in children including oral anticoagulant agents, low-dose heparin, adjusted-dose heparin, and low-molecular-weight heparin. The use of oral anticoagulants in children is problematic because serial prothrombin time testing is required to maintain levels 1.3- to 1.5-fold those of the thromboplastin control time. The pharmacokinetics of warfarin are weight and/or age dependent and infants have increased requirements. Children may also require venous access for monitoring because of the influence of multiple variables, including diet, medications, and illnesses, on drug absorption and metabolism. There are additionally the risks of hemorrhage and the potential risk of osteoporosis with long-term use. Estimates of bleeding and recurrent DVT in children receiving warfarin are 0.5 and 1.3%, respectively, per patient year.18

Low-dose heparin is administered daily based on weight and does not require serial blood testing. Peri-operative administration of subcutaneous heparin has been reported to reduce the incidence of postoperative DVT by a mean of 67 ± 4%. It has been reported that 524 (9%) of 4730 adults receiving heparin therapy experienced DVT-related complications compared with 1107 (22.4%) of 4144 patients with DVT in the control group.5 Cerrato, et al.,4 reported that the administration of mini-dose heparin (5000 IU three times daily) in 50 adult patients reduced the incidence of DVT from 34% in the control group to 6%, although there was a concomitant doubling in the rate of hemorrhage.

Adjusted-dose unfractionated heparin therapy is based on the activated partial thromboplastin time (60–80 seconds) and, although more specific, requires serial blood testing and remains the mainstay of therapeutic and prophylactic therapy in adults. Estimates of bleeding and recurrent DVT in a series of children receiving systemic doses of unfractionated heparin were 2 and 7%, respectively.19 Treatment for more than 1 month is associated with a 30% incidence of osteoporosis.8 Five percent of adult patients treated with unfractionated heparin have sustained major iatrogenic hemorrhage.25 Combination therapy involving urokinase and unfractionated heparin in children has been found to be safe and efficacious.17

The use of low-molecular-weight heparins is becoming more commonplace in children. Low-molecular weight heparins are mediated by antithrombin and are measured by antifactor Xa levels. Treatment targets antifactor Xa levels of 0.1 to 0.3 U/ml when used for prophylaxis.18

Low-molecular weight heparins do not exhibit the significant anticoagulant potency of unfractionated heparin, have greater efficacy in the treatment of venous thromboembolism, and decrease the risk of intracranial hemorrhage associated with heparin prophylaxis.24,25 They were shown to reduce significantly thrombus extension compared with unfractionated heparin in a metaanalysis of 2045 patients with DVT. Additionally, although not significant, there were trends toward decreasing recurrent thrombotic events, major hemorrhage, and overall mortality rate.16

The half-lives of low-molecular-weight heparins are greater than unfractionated heparins and simplify the management in children, providing a more predictable response to dosage.8 They are administered one or two times daily at 1 mg/kg and require no dose adjustment or blood measures. Other benefits over unfractionated heparin include the lack of interaction of diet or medications on dosing, subcutaneous administration and minimal monitoring, predictable pharmacokinetics, no increase in the rate of hemorrhage, and a decreased incidence of thrombocytopenia and osteoporosis with long-term use. Monitoring of prophylactic low-molecular-weight heparins is usually unnecessary unless there is evidence of serious underlying disease, a significant change in the patient’s weight, renal failure, or a higher risk of bleeding.18

One difficulty with the present study with regard to recommendations is the duration of the study period and the small number of patients. Whereas data pertaining to risks in adults are prevalent, those regarding children are scarce; however, certain considerations can be made. Children with cerebral ischemic events,24 spinal instrumentation,25 malignant brain tumors, SCI,12,24 trauma with neurological compromise, and a family/patient history of thrombotic disorder2 should be evaluated for DVT, and prophylactic anticoagulation therapy should be considered if presenting signs or symptoms are noted. In children with central venous catheters, the relative risk was 39.9 and the absolute rate was 28.6 per 1000 discharges.26 Children in whom long-term central lines are present should be screened for DVT and potentially receive routine prophylactic treatment.

Based on findings reported in the literature and those of the present series, the efficacy and risk/benefit ratio for IVC filter placement, urokinase and tPA therapy in children with DVT remain unclear. Because of the likely variation in serum levels and need for frequent serum testing, oral anticoagulant agents, or coumarin therapy, are a more difficult treatment regimen for younger children and should not be a first-line of therapy. Clinical data for oral therapy in neonates and young children remain incomplete.

Low-molecular-weight heparins do not exhibit the significant anticoagulant potency of unfractionated heparin, have greater efficacy in the treatment of DVT, decrease the risk of intracranial hemorrhage, possess longer half-lives than unfractionated heparins, and simplify management in children, thus ensuring a more predictable response to dosage and a decreased need for monitoring.

Conclusions

The diagnosis of DVT can be difficult in children admitted to the neurosurgical service because the underlying illnesses may mask common presenting signs and symptoms. The clinical presentation is the least effective measure of the disorder because approximately 50 to 60% of patients with DVT are clinically asymptomatic.12 As noted, the presence of central venous lines and prothrombotic disorders are the most significant risk factors reported in both the pediatric and adult literature. Clinical presentation, compression and duplex ultrasonography, and contrast-based venography constitute the three most commonly performed diagnostic tests. We recommend ultrasonography as the primary diagnostic test for children because of its diagnostic sensitivity and noninvasiveness, as well as subsequent prophylaxis/treatment involving low-molecular-weight heparins for children with suspected and/or documented DVT.
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References


Manuscript received January 15, 2004. Accepted in final form April 14, 2004. Address reprint requests to: Michael L. Levy, M.D., Ph.D., 8010 Frost Street, Suite 502, San Diego, California 92123. email: mlevy@chsd.org.