Thrombosis associated with ventriculoatrial shunts

Clinical article

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Object. In this single-center study, the authors examined the clinical characteristics, risk factors, treatment strategies, and outcomes in patients with thrombosis associated with ventriculoatrial (VA) shunts.

Methods. Inpatient and outpatient charts of patients who underwent treatment and follow-up in the Hematology-Oncology Division at the authors’ institution and in whom thrombosis developed secondary to a VA shunt placement were reviewed. A complete thrombophilia work-up was performed in each patient, and these records were also reviewed. Treatment including medical and surgical management was noted and outcome data were recorded.

Results. Resolution of thrombosis was seen after anticoagulation therapy in all patients; this may be an alternative to surgical therapy.

Conclusions. Patients with VA shunts represent a unique group at risk for thrombosis. The duration of anticoagulation therapy must be individualized. However, larger studies are needed to evaluate the efficacy of screening for asymptomatic thrombosis and to investigate the role of prophylactic anticoagulation. (DOI: 10.3171/PED.2008.2.10.286)

KEY WORDS • anticoagulant therapy • thrombosis • ventriculoatrial shunt

T he introduction of CSF shunt procedures for the treatment of hydrocephalus has resulted in a decrease in the mortality rate from 80% to 15–20%.2 Ventriculoperitoneal and VA shunts are predominantly used in the treatment of various types of hydrocephalus. Various thromboembolic complications have been described with VA shunts.2,5,8,13,16,18,22 Currently, there are no standard recommendations concerning screening for risk factors or anticoagulation treatment and prophylaxis in patients after VA shunt placement. We report on 5 patients with thromboembolic complications of VA shunts who presented to our institution over the course of 1 year. We describe the risk factors, clinical presentation, hospital course, management, and outcome in these patients.

Methods

Inpatient and outpatient clinic charts of patients with documented thrombosis related to a VA shunt were reviewed after local institutional review board approval was obtained.

Demographic features, clinical presentation, risk factors and management strategies with anticoagulation were noted and outcome data reviewed. The thrombophilia workup performed in each patient included tests of antithrombin III, protein C, and protein S activity; factor V Leiden, C677T MTHFR, and prothrombin G20210A mutations; plasma homocysteine level, lipoprotein A, anticardiolipin antibodies; and lupus anticoagulant testing (Table 1).

Summary of Cases

Case 1

History and Presentation. This 20-year-old Caucasian man with meningomyelocele, hydrocephalus, and a VA shunt was admitted to our institution with difficulty swallowing and short-term memory problems. His VP shunt had been converted to a VA shunt 8 years previously, and since then he had undergone multiple VA shunt revision surgeries. Additionally, the patient had a central venous catheter that had been inserted for better intravenous access and optimal nutrition 4 years before the present admission. This was done despite the increased risk of infection and/or thrombosis, but the patient tolerated both catheters well for 4 years. On ad-
Anticoagulant therapy for ventriculoatrial shunt thrombosis

TABLE 1

Summary of patient information

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
<th>Case 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs), sex</td>
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<td>29, M Caucasian</td>
<td>9, F Caucasian</td>
<td>18, M African-American</td>
<td>21, M African-American</td>
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<tr>
<td>Thrombus location</td>
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<td>SVC, PA (PE)</td>
<td>SVC, PA (PE)</td>
<td>rt IJV</td>
<td>rt IJV</td>
</tr>
<tr>
<td>Duration of VA shunt prior to thrombus detection</td>
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<td>8 yrs</td>
<td>5 mos</td>
<td>11 yrs</td>
<td>7 yrs</td>
</tr>
<tr>
<td>Risk factors</td>
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<td>MTHFR heterozygous</td>
<td>elevated lipoprotein A, MTHFR heterozygous</td>
<td>elevated lipoprotein A</td>
</tr>
<tr>
<td>VA shunt outcome</td>
<td>continued</td>
<td>converted to VP</td>
<td>converted to VP</td>
<td>continued</td>
<td>continued but patient died of sepsis</td>
</tr>
<tr>
<td>Duration of AT</td>
<td>LT</td>
<td>LT</td>
<td>stopped after 1 yr due to thrombus recurrence; LT</td>
<td>stopped after 6 mos</td>
<td>stopped after 1 yr</td>
</tr>
<tr>
<td>Outcome of thrombosis</td>
<td>no recurrence</td>
<td>no recurrence</td>
<td>recurred after 7 mos</td>
<td>no recurrence</td>
<td>no recurrence</td>
</tr>
</tbody>
</table>

*AT = anticoagulation therapy; IJV = internal jugular vein; LT = long-term; PA = pulmonary artery; PE = pulmonary embolism.

mission, facial and bilateral upper extremity swelling was noted. An unenhanced CT scan of his head revealed findings consistent with shunt malfunction, and the VA shunt was revised.

Operation and Postoperative Course. The patient underwent a proximal revision and the parietal ventricular cathe- ter was replaced; the distal run-off checked at the time of surgery was normal and distal shunt components were not explored. One day postoperatively, he developed respiratory distress and significant worsening of his facial and extremity swelling. Transesophageal echocardiography revealed a 1.8 × 1.3-cm, nonocclusive thrombus in the right atrium close to the VA shunt. As there was no documented infection (supported by CSF and blood cultures for aerobic and anaerobic organisms) and the thrombus was around the VA shunt catheter, the central venous catheter was not removed. The patient was started on dose-adjusted, unfractionated heparin therapy (to achieve a target activated partial thromboplastin time of 60–85 seconds) followed by dose-adjusted enoxaparin (to maintain anti-Xa levels at 0.5–1 IU/ml). A thrombophilia work-up was performed and revealed the presence of homozygous C677T MTHFR mutation and normal homocysteine levels.

The patient continued to manifest facial swelling and significant color changes in his neck and upper extremities at subsequent follow-up. Repeated transesophageal echocardiography at 6 months revealed that the right atrial clot had resolved. Because his symptoms were not explained by the echocardiography findings, he underwent nuclear venography which revealed the presence of a bilateral chronic subclavian and internal jugular thrombosis. The symptoms were deemed to be secondary to postthrombotic syndrome and he was continued on prolonged anticoagulation therapy, as any further thrombosis would have an added deleterious effect on upper body venous drainage. He has not had any recurrence of thrombosis during 17 months of anticoagulant therapy.

Case 2

History and Presentation. This 29-year-old Caucasian man with spina bifida, hydrocephalus, and a VA shunt presented with increased seizure activity. In the past, he had undergone multiple abdominal procedures including a sigmoid colectomy and ileostomy secondary to celiac disease and had had his VP shunt converted to a VA shunt 8 years prior to his presentation. The patient had also had multiple episodes of shunt malfunction and infection and a history of numerous central venous catheter placements for prolonged periods for parenteral nutrition as a part of the management of short gut syndrome.

Shunt malfunction was confirmed on unenhanced CT scans, and externalization of the VA shunt was performed. The patient was noted to have swelling on the right side of his arm, neck, and face on the postoperative Day 1. A contrast-enhanced CT scan of the thorax revealed thrombosis of the right internal jugular and SVC with extension of the clot to the right atrium, and bilateral thrombosis of the bra- chocephalic and subclavian veins. Bilateral pulmonary emboli in the left lower and right middle lobes were also demonstrated.

Operation and Postoperative Course. In view of the significant thrombosis, his shunt was converted to a VP shunt. Thrombophilia evaluation revealed an elevated homocys- teine level (16.9 μmol/L; reference range 4–12 μmol/L) and the heterozygous C677T MTHFR mutation. Dose-adjusted, unfractionated heparin was started followed by dose-adjusted enoxaparin and folic acid supplementation. Although the patient had symptoms of unstable pulmonary embolism (significant hypoxia), thrombolysis was not performed because of the risk of postoperative bleeding.

The patient continued to experience significant swelling and color changes of his upper extremity, neck and face. Follow-up radiological evaluation revealed the pulmonary embolism resolution, however continued evidence of chronic thrombosis of the veins of his upper venous system was demonstrated on upper extremity venography and Gd-enhanced MR images (Figs. 1 and 2). He was also deemed to have significant postthrombotic syndrome and was continued on long term anticoagulation (12 months). He has not had any recurrence of thrombosis. His VP shunt is still in place 23 months after it was reinstituted.
Case 3

History and Examination. This 9-year-old Caucasian girl with congenital hydrocephalus and VA shunt presented with increasing headaches and irritability. The patient had congenital hydrocephalus that required VP shunt placement at birth that was converted to a VA shunt 5 months prior to current admission. A unenhanced CT scan of her head confirmed shunt malfunction and she underwent revision surgery. During the procedure it was noted that both the intracranial and venous pressures were increased. A 2D echocardiogram was therefore obtained which revealed the presence of a 1 × 3-cm thrombus in the distal SVC. Because of her 3-day history of shortness of breath prior to admission, a contrast-enhanced thoracic CT scan was also performed, and revealed findings consistent with pulmonary embolism. On the CT scan a thrombus was identified within the SVC and right brachiocephalic vein.

A thrombophilia work-up revealed the MTHFR C677T heterozygous variant with normal homocysteine levels. The patient was started on dose-adjusted, unfractionated heparin followed by dose-adjusted enoxaparin for 12 months. An interval CT scan obtained after 6 months revealed resolution of the thrombosis. Anticoagulation therapy was stopped after 1 year.

Operation and Postoperative Course. Seven months after the anticoagulation therapy had been stopped, the patient presented with high recurrent fevers of 4 weeks’ duration and was investigated for fever of unknown origin. Initial 2D echocardiography yielded normal results, however a contrast-enhanced chest CT scan revealed the presence of a large thrombus close to the VA shunt and extending from the SVC into the right atrium. Because we suspected that the thrombus was infected, the patient underwent open cardiac surgery with removal of the intracardiac thrombus, and was treated with 6 weeks of antibiotic therapy. A percutaneous intravascular central catheter was inserted to facilitate antibiotic administration. Three days after its insertion the patient developed acute pain and swelling in her left arm and thrombosis of the left brachiocephalic vein was diagnosed on venography. In view of her significant thrombotic history, the VA shunt was converted to a VP shunt. Evaluation after 3 months revealed resolution of the left brachiocephalic vein thrombosis, but the patient continues on prolonged anticoagulant therapy because of history of recurrent thrombosis, and her VP shunt continues in situ 12 months after it was reinstituted.

Case 4

History and Examination. This 18-year-old African-American man with hydrocephalus and a VA shunt was admitted to our institution with a 4-day history of increased headaches and emesis, and a 1-day history of fever. His medical history was significant for hydrocephalus after intraventricular hemorrhage related to his premature birth. His VP shunt was converted to a VA shunt when he was 7 years of age, and he had suffered multiple episodes of shunt infection and malfunction.

Operation and Postoperative Course. The VA shunt was externalized and broad-spectrum antibiotic therapy was initiated. After treatment of the infection, the VA shunt was reinserted. On the second postoperative day the patient developed respiratory distress and neck and right arm swelling. Doppler ultrasonography of the neck revealed a thrombus in the right internal jugular vein. Contrast-enhanced CT scanning of the thorax did not reveal pulmonary embolism. A thrombophilia work-up showed high levels of lipoprotein A, normal homocysteine levels, and heterozygosity for the C677T MTHFR mutation. The patient was started on dose-adjusted, unfractionated heparin followed by enoxaparin therapy for 6 months.

Doppler ultrasonography of his neck after 6 months revealed resolution of the internal jugular vein thrombus, and anticoagulation therapy was discontinued. He has had no
recurrence of thrombosis and has no evidence of post-thrombotic syndrome 20 months after stopping anticoagulant therapy.

Case 5

History and Examination. This 21-year-old African-American man with a VA shunt was admitted with headache, nausea, vomiting, and a high tactile temperature. He had had postmeningitis hydrocephalus at age 12, which required VP and lumbar shunt placement, and had experienced recurrent proximal malfunctions related to his small, slit-like ventricles and isolated temporal horn. The literature and our experience in recent years have supported the simultaneous use of lumbar and ventricular shunts in patients with these anatomical features to drain the isolated component of the ventricular system. The VP and lumbar shunt were converted to a VA shunt when the patient was 17 years of age.6,11,19

Operation and Postoperative Course. His medical history was characterized by multiple shunt revisions and infections. An unenhanced head CT scan revealed findings consistent with shunt malfunction and the patient underwent proximal revision of the VP shunt. A day after the procedure he became tachypneic with decreased oxygen saturation. A contrast-enhanced thoracic CT revealed left lower and right upper lobe pulmonary emboli; there was no other evidence of thrombosis. A thrombophilia work-up revealed high levels of lipoprotein A. Dose-adjusted unfractionated heparin was initiated followed by dose adjusted enoxaparin for 12 months.

The patient received 12 months of anticoagulation therapy. A follow-up CT scan of his thorax revealed resolution of the pulmonary embolism. Although the patient had no recurrent thrombotic events, he died of fulminant sepsis 21 months after anticoagulation therapy had been discontinued. At autopsy, there was no evidence of thrombosis.

Discussion

When clinical conditions do not permit the use of the peritoneal cavity as the distal site of CSF absorption, VA shunts are an alternative used by most neurosurgeons in the treatment of hydrocephalus.22 In 504 patients with ventricular shunts who have attended follow-up at our center, 91 (18%) had the distal catheter end in the atrium.

Since the introduction of the VA shunt for hydrocephalus treatment by Nulsen and Spitz15 in the late 1940s, several thromboembolic complications have been reported.16,22–24 Although rare, their presentation is potentially fatal. Thromboembolic complications present clinically in 0.3% of patients, whereas autopsy series reveal an incidence up to 60%.4,17 In particular, the incidence of clinically significant pulmonary emboli is 3.2% in patients with VA shunts; however, these are encountered in 50–100% of patients with VA shunts at postmortem examination.10 This complication, unique to VA shunts, fall into 2 principal groups: cardiac and pulmonary thromboses.4,10 A right atrial thrombus is the most common cardiac complication described. Currently, the presence of a VA shunts constitutes a risk factor for the development of chronic thromboembolic pulmonary hypertension.2 Based on this evidence, several studies have concluded that VA shunts should be reserved for patients in whom an intraabdominal pathological entity precludes peritoneal shunt placement.24

Pathophysiology of VA Shunt Thrombosis

Several hypotheses have been put forth to explain the development of thromboembolic events. The catheter may damage the endothelial surface and may also alter the laminar flow of the blood in the atria or the SVC. The catheter may also act as a foreign body, inducing formation of a fibrinous coating on the distal end of the catheter with subsequent formation of a thrombus.10 It is also suggested that the release of cerebral thromboplastin in the cerebral ventricle and transport in the VA shunt could contribute to activation of the coagulation cascade and subsequent thrombus formation.10 It remains unclear whether shunt infection plays a role in the development of a thrombus,10,28 but certainly it is known that bacteria attract complement and subsequently clotting factors. Coating the shunt tube with silicone has failed to decrease the incidence of thrombotic events significantly.4,23 Thromboembolic complications can also be decreased by positioning the catheter in the right atrium rather than the SVC.4,16,20 It is our practice to place the distal atrial catheter at dorsal spinal levels 5 and 6, roughly corresponding to the SVC atrial junction. Positioning is confirmed at the time of surgery with fluoroscopy and adjusted for any abnormal spinal curvature.

Thrombophilia in the Patients With VA Shunt Thrombosis

The presence of a VA shunt itself is a risk factor for thrombosis. Whether patients should be screened for additional thrombophilic markers is not known. In 1 series of intracardiac thrombosis, all 3 patients with VA shunts who were screened for the factor V Leiden mutation were found to have a heterozygous mutation.1 In our case series, thrombophilic conditions were present in 3 of 5 patients (hyperhomocysteinemia in 1 patient and elevated lipoprotein levels in 2). Another genetic factor that has been extensively studied over the last decade is a polymorphism in the MTHFR gene, which encodes an enzyme involved in homocysteine metabolism that converts folate, a cofactor for homocysteine conversion, into 5-methyltetrahydrofolate. In this mutation, a common C to T substitution at position 677 renders the enzyme thermolabile. Homozygotic individuals have a > 50% reduction in enzyme activities and the effect of reduced MTHFR activity may lead to hyperhomocysteinemia in the presence of low folate intake. Interestingly, 4 of our 5 patients were found to have the C677T MTHFR mutations (3 heterozygous and 1 homozygous). Only 1 patient had a high homocysteine level (Case 2). The contribution to thrombosis by the presence of a MTHFR C677T mutation without accompanying hyperhomocysteinemia in the other 3 patients is debatable.

Treatment of VA Shunt Thrombosis

There are currently no standard recommendations for treatment of VA shunt-related thrombosis. A high failure rate with medical treatment has been reported.26 In the past, medical treatment by itself was thought to be inadequate for management of VA shunt-related thrombosis. The simple withdrawal of the distal end of a VA shunt on which there is a thrombus is contraindicated as it would free the
thrombus with risk of embolization. Thus in the past, surgical removal of the thrombus has been the treatment of choice. However, surgical removal of a thrombus is difficult and has a mortality rate of 21–67%. We were able to demonstrate that VA shunt–related thrombi can be managed with anticoagulant therapy alone. In all of our patients, we documented resolution of thrombi with anticoagulants alone. One patient (Case 3) underwent surgical removal of the thrombus when an infected thrombus was suspected on recurrence.

The duration of anticoagulative therapy is another matter of debate, and the optimal time for discontinuing anticoagulation is not known. In our series, patients with pulmonary emboli received therapeutic anticoagulation for 1 year. Two patients (Cases 1 and 2) continued on prolonged anticoagulative therapy because of significant postthrombotic syndrome. It was deemed that any thrombosis of the collateral circulation would lead to progression of postthrombotic syndrome and could adversely affect the cerebral venous drainage, leading to increase in the hydrocephalus. However, whether anticoagulation therapy should be continued in the presence of an indwelling VA shunt is currently unknown. Presumably, in patients with documented thrombosis an approach similar to central venous catheter–related thrombosis may be taken. In general the recommendations are to treat catheter-related thrombosis for 3 months with anticoagulation therapy followed by either removal of catheter (if possible), or continued anticoagulation therapy. Removal of the VA shunt may not be an option in all patients. Interestingly, in 2 of our patients we were able to convert the VA shunt back to a VP shunt (Cases 2 and 3). In the other 3 patients who continued with VA shunts, 1 patient had a recurrence of SVC thrombosis following cessation of anticoagulation therapy (Case 3), while 2 patients (Cases 4 and 5) did not.

In the present study, our patients underwent treatment with low-molecular weight heparin (enoxaparin) as many were taking multiple medications with the potential for drug interactions with coumadin. The ease of anticoagulation reversal for immediate shunt revision was also considered. The effect of enoxaparin on the bone density of patients is unknown; due to their nonambulatory status, many neurosurgical patients may be particularly at risk for bone fractures. Interestingly, only 1 patient had symptomatic thrombosis at presentation. All 5 patients presented with shunt malfunction and the patient in Case 3 presented with a fever of unknown origin at the time of recurrence. It is unclear whether the shunt revision caused the thrombosis or whether the thrombosis resulted in the shunt malfunction. Also of interest, all of the patients in the study group had a significant decrease in shunt malfunctions during the anticoagulation therapy (Table 2). It is possible that the formation of a small, asymptomatic thrombus can lead to shunt malfunction in patients with VA shunts. These data are comparable to the reported experience with central venous catheters in cancer patients: deep venous thrombosis has been associated with catheter dysfunction and infection in patients with cancer and central catheters. It is speculated that by preventing further clot formation anticoagulation therapy may prevent shunt malfunction. This raises the question of whether patients with VA shunts and recurrent malfunctions be screened for asymptomatic thrombi, and/or be treated with prophylactic anticoagulation therapy.

### Summary of episodes of VA shunt thrombosis and infection

<table>
<thead>
<tr>
<th>Case No.</th>
<th>BAT Malfunction</th>
<th>DAT Malfunction</th>
<th>AAT Malfunction</th>
<th>BAT Infection</th>
<th>DAT Infection</th>
<th>AAT Infection</th>
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<tbody>
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</tr>
</tbody>
</table>

* The BAT period lasted as long as the duration on anticoagulant therapy, unless otherwise specified. Abbreviations: AAT = after AT; BAT = before AT, DAT = during AT; NA = not applicable (because the patient continued to be on AT during follow-up).
† The VA shunt was converted to a VP shunt when AT was started.
‡ Patient had conversion of VP to VA shunt 5 months prior to thrombotic event. The second value is the number of events during the second period of AT.

### Conclusions

Patients with VA shunts represent a unique group at risk for thrombosis. Our study is limited by the small number of patients studied. Although there have been occasional case reports of patients receiving anticoagulation therapy, we believe that this is the largest case series of patients with VA shunts who received successful anticoagulation therapy alone and had a systematic work up for coexisting thrombophilic markers. Specific treatment protocols to address the duration and choice of anticoagulation medication are needed for patients with VA shunt. In patients who have had a prior thrombosis and in whom the VA shunt cannot be converted to a VP shunt, long-term anticoagulation therapy may be considered on an individualized basis. Larger studies are needed to evaluate the efficacy of screening for asymptomatic thrombosis, and to investigate a possible role for prophylactic anticoagulation therapy.

### Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

### References

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Accepted June 18, 2008.

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