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Cerebral Sinus Thrombosis in a Trauma Patient after Recombinant Activated Factor VII Infusion

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SEVERAL investigators have reported the astonishing effect of recombinant activated factor VII (rFVIIa) in trauma patients with diffuse bleeding. Currently, rFVIIa is approved for the treatment of patients with hemophilia with inhibitors to factors VIII and IX. Conditions with increased thromboembolic risk, including trauma, extensive tissue damage, sepsis, arteriosclerosis, and disseminated intravascular coagulation, may be considered contraindications for the drug. Thrombotic complications in trauma patients are rarely observed. To our knowledge, this is the first report of a patient who experienced a cerebral sinus thrombosis in the posttraumatic period after rFVIIa administration.

Case Report

A 19-yr-old man was involved in a frontal motorbike accident. He had an open shaft fracture of the femur, pneumothorax, and lung contusions. A small frontal brain contusion was only visible on a follow-up computed tomographic (CT) scan, without any initial neurologic impairment.

After the pneumothorax was sufficiently drained, the patient underwent surgical reposition of his thigh. Stabilization was achieved with external skeletal fixation. The intense bleeding was under control after reposition and intermittent tamponade. No damage of major vessels was found. An extensive supracondylar hematoma was drained.

Twelve hours after stabilization of the fracture, the patient showed signs of bleeding. Before and during surgical revision of the thigh, he received 16 units of erythrocytes, 11 fresh frozen plasmas, 8 single-donor platelet concentrates, and a single bolus dose of 240 KU (60 μg/kg body weight) rFVIIa. Again, no damage of major vessels was found. Bleeding stopped promptly after administration of rFVIIa. During the operation, an intramuscular hematoma was drained, and fasciotomy was performed on the thigh and lower leg. After this, the patient was stable, with a hemoglobin concentration at 7.5–8 mg/dl.

Because of the patient's pulmonary impairment, it was difficult to wean him off the respirator. After return to spontaneous ventilation, he showed changing levels of consciousness. A follow-up CT scan of the brain was performed at day 5, which showed a small frontal contusion without any space-occupying character (fig. 1A).

In the second week, the patient started to present signs of infection of the fracture site. His body temperature peaked on day 13 up to 39.7°C and decreased immediately after surgical revision and débridement. The leukocyte count at that time was 15.1×10^9/l, and C-reactive protein, with a maximum of 236 mg/l on day 9, had decreased to 100 mg/l on day 15. Reactive thrombocytosis occurred, with a maximum of $1{,}080 \times 10^9$/l on day 19.

On day 15, the patient presented with a unilateral dilated pupil with remaining prompt reaction to light, spontaneous inward rotation, extensions of the upper and lower limbs, and vomiting despite drained gastric tube. Native and contrast-enhanced CT scans were performed to rule out septic dissemination and did not show any pathologic findings (fig. 1B). Bacterial meningoencephalitis was ruled out by lumbar puncture. A possible systemic herpes simplex infection after the labial lesions was treated prophylactically with acyclovir until viral genome testing results were found to be negative by polymerase chain reaction.

After another 12 h, the patient again showed signs of impaired brainstem function. A second CT scan showed slightly dilated lateral ventricles. After the insertion of ventricular drainage, intracranial pressure did not increase.

Because of the persistent impaired consciousness, another follow-up CT scan was performed on day 21, and hypodense areas in the anterior parts of both thalami were found (fig. 1C). Bilateral thalamic edema after thrombosis of internal cerebral veins was considered to be the most likely diagnosis, but to visualize the thrombus and to rule out other causes of thalamic hypodensities, such as ischemic infarction, a magnetic resonance imaging study was performed on the same day. The corresponding areas of both thalami showed signs of edema (figs. 2A–C) but no contrast enhancement. Signal intensity in diffusion-weighted imaging was slightly increased, probably because of T2 sensitivity of the sequence, but not to the extent typically seen in ischemic infarction. There were no signs of intracerebral hemorrhage.

The thrombus itself was found in the proximal part of the straight sinus, obstructing the confluence of the inferior sagittal sinus and the great cerebral vein of Galen. It was surrounded by a narrow stripe of contrast media (fig. 3A). Phase contrast magnetic resonance angiography showed a remaining flow signal in the area of the thrombus (fig. 3B).

To achieve differentiation of the thrombus against a venous anomaly, conventional angiography was performed on the following day. In late venous images, sustained contrast was detected in the great cerebral vein of Galen, the internal cerebral veins, and the thalamostriate veins (fig. 3C), making venous congestion the most probable cause for thalamic edema.

Intravenous anticoagulant therapy was initiated, and within 3 weeks, the neurologic situation improved gradually (figs. 2B and C).

Discussion

In several case reports[1,2] and small studies,[3] antihemorrhagic effects of recombinant activated factor VII (rFVIIa) has been described in diffuse hemorrhage of trauma and surgical patients. Massive transfusion dilutes coagulation factors and impairs platelet number and function. Excessive treatment with fluids such as hydroxyethyl starch preparations might directly compromise coagulation. Concomitant hypothermia causes slowing of enzymatic

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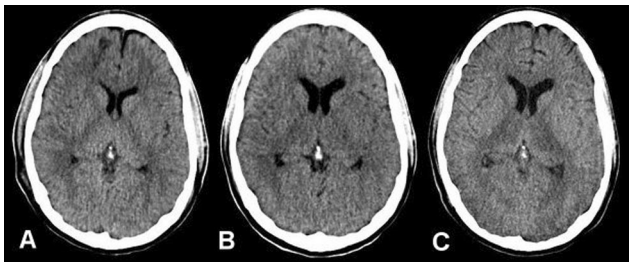

Fig. 1. Development of bithalamic edema in cranial computed tomography. (*A*) On day 5 after trauma, both thalami are of normal density and well delineated against the internal capsule. A hypodense area in the right frontal lobe is a contusional lesion. (*B*) Because the neurologic status of the patient had deteriorated on day 15 after admission, this computed tomographic scan was performed to rule out septic encephalitis after a febrile episode. There was no sign of inflammatory disease on the contrast-enhanced studies not shown here. With our knowledge of the further progress of the disease, a decrease in density of both thalami and a reduction of contrast between thalami and internal capsule can already be seen in this scan. (*C*) Because on this computed tomographic scan performed on day 21 both thalami are clearly hypodense, a cerebral sinus thrombosis was suspected. A magnetic resonance imaging study was performed on the same day to differentiate between an edema caused by sinus thrombosis and ischemic cerebral infarction.

activities of the coagulation cascade and dysfunction of platelets. Release of procoagulant substances from ruptured tissues leads to a complex consumptive coagulopathy with enhanced fibrinolysis. Metabolic abnormalities, such as acidosis and hypocalcemia, further deteriorate coagulation.

Under these circumstances, diffuse bleeding often persists, despite apparently adequate surgical procedures and treatment with blood products and conventional hemostatic agents. In single cases[1] and small study groups,[2] rFVIIa was successfully given to achieve hemostasis in severe bleeding, without previous coagulopathy. Thromboembolic complications have been described, such as venous thrombosis,[4] myocardial infarction,[5] and disseminated intravascular coagulation.[6,7] The described thrombotic events often have occurred in the context of preexisting risk factors, *e.g.*, crush injury, tissue necrosis, septicemia, atherosclerosis, or previous administration of activated prothrombin complex, making it difficult to pinpoint the contribution of rFVIIa to these adverse events.

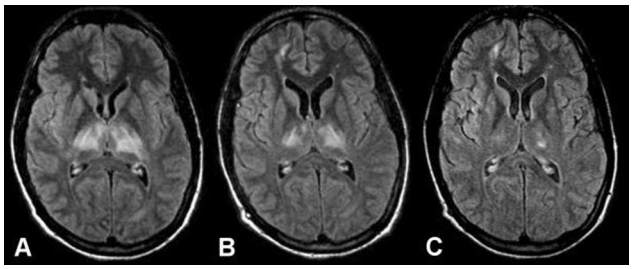

Fig. 2. Time course of the bithalamic edema in magnetic resonance imaging, fluid attenuated inversion recovery sequences, repetition time = 9,000, and echo time = 110. Small areas of high signal intensity in the right frontal lobe indicate postcontusional damage, as already seen on the corresponding computed tomographic scans. (*A*) Magnetic resonance imaging on day 21 after admission shows hyperintense bithalamic edema, corresponding to the computed tomographic scan in figure 1C, which led to further imaging. Follow-up magnetic resonance imaging on day 27 (*B*) and day 40 (*C*) show a visible reduction in the size of the edema, matching the clinical restitution.

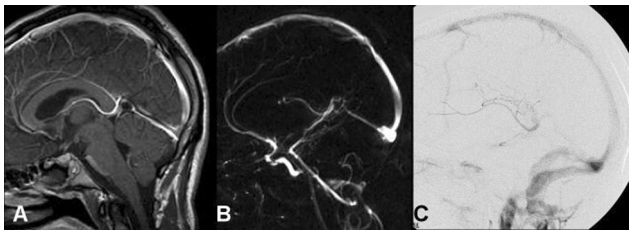

Fig. 3. (*A*) Sagittal T1-weighted magnetic resonance imaging at repetition time (TR) = 500 and echo time (TE) = 17 after intravenous administration of gadolinium (III) diethyltriaminepentaacetic acid shows the thrombus in the straight sinus near the confluence of the great cerebral vein of Galen and the inferior sagittal sinus, surrounded by a narrow trace of contrast media. (*B*) Some blood flow around the thrombus leading to an incomplete occlusion can be detected in phase contrast magnetic resonance angiography at TR = 86 and TE = 10, which is part of the routine protocol for cerebral sinus thrombosis. (*C*) Retention of contrast media in the great cerebral vein of Galen, the internal cerebral veins, and the thalamostriate veins can be clearly demonstrated in the venous phase of conventional angiography, proving the hemodynamic relevance of the occlusion for development of thalamic edema.

In our patient, obvious clinical signs of his cerebral sinus thrombosis became evident 14 days after administration of rFVIIa, when the patient presented with a unilateral dilated pupil and spontaneous inward rotation. With a half-life of rFVIIa of approximately 6 h, a direct relation seems rather unlikely. However, because cerebral sinus thrombosis in the age group of our patient and with the presented trauma pattern is rare and extensive clinical experience with rFVIIa is lacking, we are considering a relation to the administration of rFVIIa, in contribution with an endothelial lesion of the cerebral sinus caused by the mild brain injury. With the exposure of subendothelium after the small blood vessel injury, cell-bound tissue factor may be exposed and may cause formation of microthrombus. Without enhancement of the coagulation by rFVIIa, the microthrombus might have resolved quickly, without any clinical recognition. With the administration of rFVIIa and the generation of a high thrombin burst, a more stable clot was probably created, not resolving until day 14 when, under septic conditions, the coagulation became activated. When toward day 14 the patient's septic situation aggravated, the thrombus may have increased in volume, or smaller thrombi may have occluded the remaining drainage beside the initial thrombus, compromising the venous drainage of the thalamic region.

A similar delay between rFVIIa administration and thrombosis formation was seen by Van der Planken *et al.*[4] in a hemophilia A patient with inhibitors and severe infectious disease. This patient experienced a distal deep

venous thrombosis 18 days after rFVIIa transfusion. Also, d'Oiron *et al.*[6] described a pulmonary embolism of the lung 5 days after discontinuation of rFVIIa infusion.

Despite the promising beneficial effect of rFVIIa for hemostasis in massively bleeding trauma patients, the thrombotic risk of the drug must be kept in mind. Therefore, close monitoring is necessary for early identification of thrombotic complications.

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Argatroban as Anticoagulant in Cardiopulmonary Bypass in an Infant and Attempted Reversal with Recombinant Activated Factor VII

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HEPARIN-INDUCED thrombocytopenia (HIT) is an infrequent complication of heparin therapy.[1] A unique problem arises in patients with HIT who need anticoagulation, especially if urgent cardiac surgery is planned. We report a case of HIT in an infant in which Argatroban (GlaxoSmithKline, Middlesex, UK) was used as anticoagulant during cardiopulmonary bypass (CPB) and the unsuccessful use of recombinant activated factor VII (rFVIIa) to reverse the anticoagulant effects postoperatively.

Case Report

A 9-month-old male patient (weight, 5.5 kg) had undergone complete repair of a transposition of the great arteries, a ventricular septal defect, and a pulmonary stenosis at 7.5 months of age by means of CPB and heparin. He was readmitted to the hospital 2 weeks after discharge with congestive cardiac failure and mediastinitis. An echocardiogram showed large vegetations in the right ventricle in the vicinity of the homograft, and positive blood culture results were obtained. A diagnosis of endocarditis was made, and a Broviac catheter was inserted. His platelet count decreased from 60,000 cells/mm^{-3} to 15,000 cells/mm^{-3} within 2 days after receiving heparin flushes in the Broviac catheter. An HIT assay, consisting of a heparin-dependent platelet activation assay, as well as an enzyme-linked immunosorbent assay (GTI, Brookfield, WI), yielded positive results. The diagnosis of HIT was made, and all heparin was immediately stopped. An Argatroban infusion was started at 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after a bolus dose of 200 μg/kg. The infusion rate was adjusted to keep the activated partial thromboplastin time at 1.5–2 times the normal value. Despite antibiotic treatment, the vegetations in the right ventricle remained unchanged. It was decided to reoperate to remove the Gortex (W. L. Gore & Associates, Newark, DE) hood from the homograft and clear out any vegetation. One week after stopping heparin administration, the platelet count had recovered to 212,000 cells/mm^{-3}.

The Argatroban infusion was stopped 4 h preoperatively to allow placement of lines and to minimize blood loss before CPB. Baseline activated clotting time (ACT) was 160 s. A total of 750 μg/kg Argatroban was administered in three divided doses over 50 min to increase the ACT to more than 400 s. Immediately on initiation of bypass, the ACT was longer than 999 s, and the Argatroban infusion, which had been started after the initial bolus, was stopped. The ACT remained at more than 999 s for the next 2 h. The total bypass time was 1 h. The patient was weaned from bypass without difficulty. At this point, hemostasis was difficult to obtain, and a total of 250 ml (45 ml/kg) fresh frozen plasma and 2 units platelets were administered over 1 h. This reduced the ACT to 394 s, but hemostasis remained inadequate. After consultation with a hematologist, two doses (90 μg/kg each) of rFVIIa (Niastase; Novo Nordisk, Bagsvärd, Denmark) were administered 20 min apart. There was no significant improvement in hemostasis clinically or in the ACT after administration of rFVIIa. (The ACT decreased to 329 s after the second dose.) An additional 20 ml/kg fresh frozen plasma was administered over the next hour. Serial ACTs, repeated every 30 min after the rFVIIa, were 329, 315, 285, and 208 s. Satisfactory hemostasis was eventually achieved 2 h after administering the rFVIIa, and the patient was transported to the intensive care unit in a stable condition.

A total of 500 ml (90 ml/kg) packed erythrocytes, 2 units platelets, and 375 ml (65 ml/kg) fresh frozen plasma were administered intra-

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operatively. Bleeding from the chest tube totaled 60 ml in the first 12 h postoperatively. There were no thrombi noticed in the bypass circuit postoperatively. The ACT reached a control value of 160 s at 10 h after the initial doses of Argatroban. The Argatroban infusion was restarted after 12 h and transitioned to Coumadin (Du Pont Pharma, Mississauga, Ontario, Canada) after 5 days. The patient was transferred out of the intensive care unit after 1 week. The results of an HIT assay repeated after 1 month remained positive.

Discussion

This is the first reported case in which Argatroban has been used as an anticoagulant during cardiac surgery in an infant with HIT, a recognized complication of heparin exposure that is rarely reported in children.[1,2] The cornerstone of treating a patient with HIT is the discontinuation of all heparin. Heparin cessation alone may not be effective in preventing thromboembolic events,[3] and alternative anticoagulants should be considered because thromboembolism often occurs when the platelet count rebounds. An Argatroban infusion was started in our patient because he was considered to be in the acute phase of HIT and at high risk of a thromboembolic event. However, discontinuation of heparin poses another challenging problem in patients with HIT who need subsequent cardiac surgery. Alternative anticoagulants include danaparoid sodium, lepirudin, ancrod, Argatroban,[4] and recently also bivalirudin.[5] Routine coagulation tests cannot be used to monitor the anticoagulant effect of danaparoid, but the ecarin clotting time does reliably monitor the anticoagulant effect of lepirudin and bivalirudin. The pharmacokinetic profile of bivalirudin in particular makes it an attractive alternative in a situation in which heparin is contraindicated.[5]

Argatroban is a synthetic small-molecule direct thrombin inhibitor derived from L-arginine.[6] It inhibits free and clot-bound thrombin, the interaction with thrombin being reversible. As with danaparoid and other direct thrombin inhibitors, Argatroban has no specific antidote, but it nevertheless has potential advantages. It has a relatively short half-life (40–50 min). It does not require antithrombin III as cofactor, and it undergoes hepatobiliary excretion, making its use safe in renal failure. In addition, its activity can be measured with routine coagulation tests, such as activated partial thromboplastin time and ACT.[7]

Argatroban has been used in vascular surgery, including left heart assist,[8] in adult and pediatric extracorporeal membrane oxygenation,[9,10] and also in off-pump coronary artery bypass surgery.[11] Argatroban has also been used successfully as an anticoagulant in CPB studies in a dog model.[12] In addition, there are case reports of its successful use as the anticoagulant in CPB in adult patients with antithrombin III deficiency[13] and with HIT.[14] Furukawa *et al.*[13] recommend an ACT of more than 400 s when using Argatroban for cardiac surgery. They used a bolus of 0.1 mg/kg, followed by a continuous infusion of 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In our case, we needed to administer a total of 750 μg/kg to increase the ACT to more than 400 s. Interestingly however, immediately on initiating CPB, the ACT in our patient was more than 999 s. This probably reflected abrupt hemodilution on the bypass circuit; the commonly seen increase in ACT on initiating bypass[15] is perhaps exacerbated when Argatroban is used.

Although rFVIIa is not indicated for the reversal of Argatroban, there are successful reports of the use of rFVIIa to treat coagulopathy and bleeding after CPB in infants and children.[16,17] There was no significant improvement clinically in our patient after administration of rFVIIa or in the ACT values taken in the next 2 h. The reduction in ACT over the 2-h period probably largely represented metabolism of the drug as well as additional fresh frozen plasma administration. There is no documented clinical experience with the reversal of direct thrombin inhibitors with rFVIIa, but our observation in this case corresponds to laboratory data in which rFVIIa at very high doses failed to fully restore hemostasis or produce a significant reduction in blood loss in anesthetized rats treated with a direct thrombin inhibitor, melagatran.[18] Among the possibilities are that rFVIIa will not work or that the dose was inadequate given what seems to have been an excessive anticoagulation effect of Argatroban. The only clinically proven efficacy of rFVIIa is for hemophilia, but when diagnosis and treatment of specific coagulation defects fail to correct coagulopathy, it may be reasonable to use rFVIIa as rescue therapy, as was the case in our patient.[19] Clinical trials are needed to address the potential reversal of direct thrombin inhibitors with rFVIIa.

Our patient experienced major bleeding during surgery and needed infusion of large volumes of fresh frozen plasma, packed erythrocytes, and platelets. This case illustrates the potential risks of using new anticoagulants for cardiac surgery. Although it was not an option in our patient because the HIT assay results remained positive after 1 month, repeated use of unfractionated heparin remains the preferred approach to anticoagulation in patients with HIT who need repeat cardiac surgery, provided that HIT antibodies are no longer detectable.[20,21]

We conclude that Argatroban is a potential alternative anticoagulant for use during CPB, although formal pharmacokinetic studies are needed in infants and small children to establish a safe and optimal dosing regimen. Careful titration of Argatroban to a therapeutic ACT, activated partial thromboplastin time, or possibly ecarin clotting time is advised, bearing in mind a possible unpredictable ACT response due to hemodilution on initiating CPB in infants and small children. rFVIIa also did not reverse the anticoagulant effect of Argatroban in our patient.

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Epidural Granuloma and Intracranial Hypotension Resulting from Cervical Epidural Steroid Injection

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CERVICAL epidural steroid injections (CESIs) are generally used for the treatment of radiculopathy and pain. Other reasons cited for using CESIs include postlaminectomy syndrome, bulging cervical disc, and brachial plexitis.[1] Side effects of CESIs include stiff neck, flushing, wet tap, failed block, vomiting, upper extremity motor weakness, and transient paresthesia.[1–2] Rare but potentially catastrophic complications of CESI can occur, such as arachnoiditis, hematoma, meningitis, and quadraplegia.[3,4] We present a case of cervical epidural granuloma and intracranial hypotension after administration of epidural triamcinolone acetonide (Kenalog; Bristol-Myers Squibb, Princeton, NJ).

Case Report

A previously healthy 39-yr-old woman presented with a 2-week history of lower neck pain radiating to the left axilla and across the left side of the chest. Initial therapy consisted of tapering use of oral methylprednisolone, cyclobenzaprine, and valdecoxib. One week later, the patient experienced numbness of the left hand. Magnetic resonance imaging (MRI) revealed a herniated disc at C6–C7, with protrusion into the left C7 axillary sleeve.

The patient underwent a series of three CESIs, each 2 weeks apart, over the next 6 weeks at an outside hospital. According to the medical records and patient recollection, all the blocks were performed at the C6–C7 interspace, with the patient sitting upright and with use of an 18-gauge Tuohy needle. The neck was flexed and independent of support. Sedation was with 3 mg intravenous midazolam. The needle was inserted and advanced using a hanging drop technique. Fluoroscopy was used. Results of aspiration were negative for blood and cerebrospinal fluid (CSF). Contrast was injected, followed by 0.5% lidocaine and 60 mg triamcinolone, for a total volume of 5 ml, for the first two blocks.

Within a week after the first block, the patient experienced headaches, night sweats, and constant upper cervical neck pain. During the third and final block, the patient experienced a "lightning-bolt" type pain radiating down the outer aspect of the right shoulder, elbow, and fingers. The needle was promptly withdrawn, and the pain resolved. The needle was then readvanced in the same interspace, and the block was performed with 0.5% lidocaine and 80 mg triamcinolone, for a total volume of 5 ml.

Over the next 6 weeks, the patient's condition worsened. The headache and upper cervical pain became severe, and upper extremity tremor, facial flushing, upper extremity weakness, hyperreflexia of all extremities, and numbness over the anterior aspect of both thighs developed. MRI showed a fusiform anterior epidural mass effacing the thecal sac, causing mild posterior displacement of the spinal cord, with prominent distension of the epidural venous plexus. The mass enhanced with gadolinium (fig. 1; 1 month after the third epidural injection).

The patient was admitted to the hospital. Blood culture results were negative. Vertebral angiography results revealed prominent veins in the anterior epidural space in the upper cervical spine but were otherwise normal. There was no evidence of dural sinus thrombosis or arteriovenous malformation. Antibiotic therapy was initiated with in-

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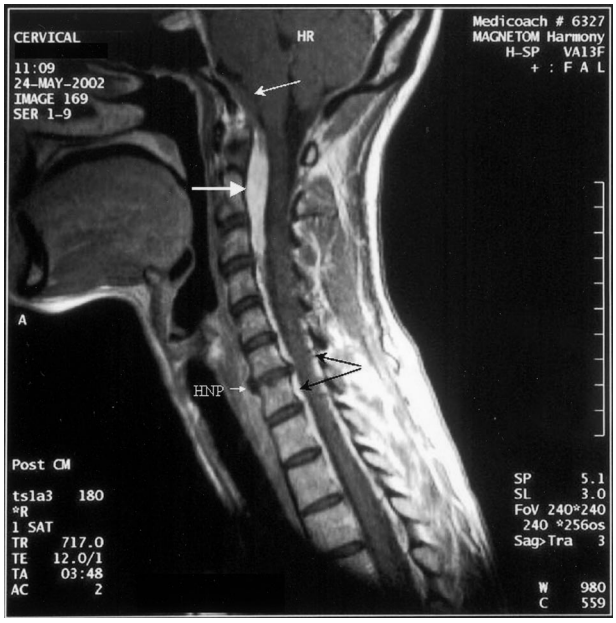

Fig. 1. Cervical magnetic resonance image, enhanced T1-weighted sagittal image. Note the anterior enhancing epidural mass (*thick white arrow*) effacing the thecal sac, causing mild posterior displacement of the spinal cord. There is abnormal enhancement of the epidural space anteriorly and posteriorly (*black arrows*) and a nonenhancing subdural collection over the clivus superiorly (*thin white arrow*). There is a C6–C7 herniated nucleus pulposus (HNP).

travenous vancomycin and ceftriaxone and oral metronidazole and continued for 1 month. Tapering oral methylprednisolone was given.

Headaches and neck pain were treated over the next 4 months with a variety of medications, including fentanyl patch and oral diazepam, and tapered to acetaminophen–propoxyphene and valdecoxib. The patient continued to experience headaches and had decreased hearing in the left ear, upper extremity tingling, and numbness. Three months later, the headaches became incapacitating and were associated with nausea. The headaches were notably worse in the sitting and standing positions.

A brain MRI with and without contrast revealed extensive uniform enhancement of the pachymeninges, prominence of cavernous sinuses, increased volume of the pituitary gland, and subdural convexity

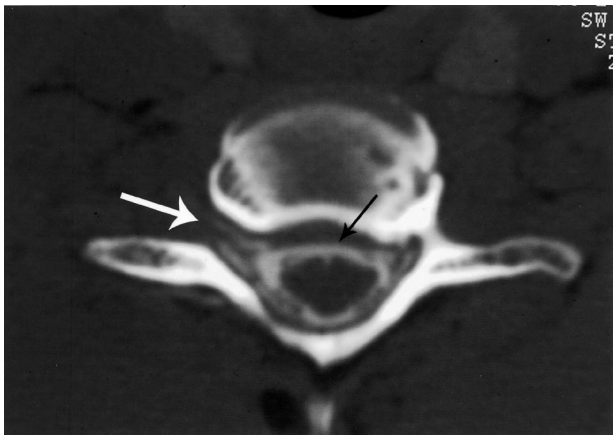

Fig. 3. Axial computed tomographic myelogram image. Extradural contrast is seen around the right C7 nerve root sleeve (*white arrow*). The thecal sac is displaced from the posterior margin of the vertebral body (*black arrow*).

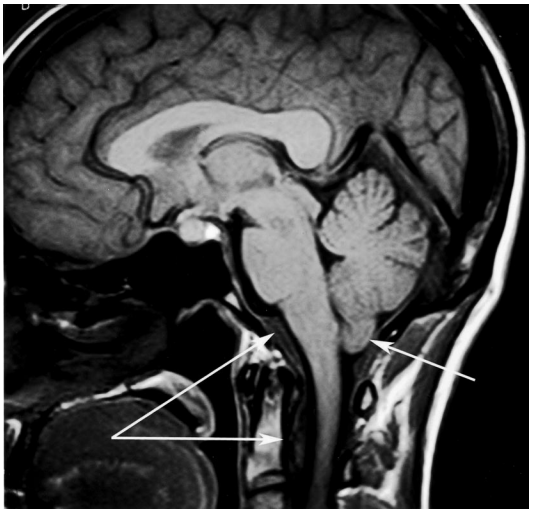

Fig. 2. Unenhanced T1-weighted sagittal image. Note the lower position of the cerebellar tonsils (*single arrow*) as compared with figure 1. There are extensive abnormal epidural and subdural collections (*double arrow*).

hygromas, consistent with reactive changes to intracranial hypotension. There were extraaxial collections along the anterolateral margins of the foramen magnum extending inferiorly, and low-lying cerebellar tonsils (fig. 2). A cervical myelogram and a computed tomographic myelogram showed an extradural leak of contrast centered on the right at the C6–C7 level. (fig. 3) There was a C6–C7 disc herniation with moderate thecal sac compression.

Ten days later, the patient underwent anterior cervical spine discectomy with autologous bone graft placement. After removing the C6–C7 disc and taking down the posterior longitudinal ligament, CSF was observed to be welling up, mostly from the right side. A blood patch with fibrin glue was constructed, and the bone graft was inserted. There was no evidence of CSF leak afterward. The patient was discharged home on the second postoperative day, free of headaches. She still experiences chronic low-grade neck pain and nonintention tremor of the right thumb. A smaller epidural mass is still present on MRI 4 months postoperatively.

Discussion

Neurologic complications after CESIs are rare but devastating. Trauma may occur as a result of epidural needle disruption of nerve fibers and can be exacerbated by intraneuronal injection into the spinal cord or spinal nerve root.[5] A granulomatous response may follow, with thickening of the dura, as occurred in the current patient. Dural puncture and possibly direct nerve injury from the needle likely occurred during the third block. Dural puncture would allow triamcinolone and its preservative to gain access into the subarachnoid space with resultant nerve damage. Substantial amounts of CSF leak led to intracranial hypotension and incapacitating postural headaches.

Intracranial hypotension is a relatively new diagnosis that has been increasingly recognized since 1991 with the advent of MRI. Patients present with orthostatic headache that is relieved by recumbency.[6] Intracranial hypotension may occur in association with dural punc-

ture during cervical epidural block, as in our patient, or it may occur from spontaneous CSF leak, most often at the level of the thoracic spine or cervical thoracic junction.[6] Spontaneous CSF leak can be associated with trivial trauma in conjunction with weakness of the meningeal sac, meningeal diverticula, and/or spondylotic spur.[6] Clinical manifestations include neck stiffness, tinnitus, ear obstruction, faintness, photophobia, nausea, and vomiting. Descent or sinking of the brain, as occurred in our patient, is due to CSF volume depletion and accounted for the low-lying cerebellar tonsils. Descent of the cerebellar tonsils may mimic type 1 Chiari malformation. Loss of CSF volume in the presence of an intact skull is compensated by intracranial and meningeal venous hyperemia.

According to the Monro-Kellie rule, there is an inverse relation of CSF volume and intracranial blood volume such that if CSF volume decreases, intracranial pressure is maintained by increased blood volume, particularly in the venous capacitance system.[7] Because the pachymeninges have no blood–brain barrier, diffuse pachymeningeal gadolinium enhancement occurs.[6] Other imaging abnormalities are engorgement of cerebral venous sinuses and subdural and extraarachnoid fluid collections, as shown on MRI and computed tomographic myelography in our patient at 7 months. Enlargement of the pituitary gland, decreased size of the ventricles, obliteration of prepontine or perichiasmic cisterns, flattening of the optic chiasm, crowding of the posterior fossa, and engorgement of the cervical epidural venous plexus may also occur. Traction, distortion, compression, or vascular congestion of cranial nerves may have been responsible for some of the patient's hearing symptoms. Computed tomographic myelography is the most reliable test to demonstrate CSF leak.

Early surgical treatment was deferred in our patient despite demonstration of the anterior cervical epidural mass. This was because of the patient's otherwise stable neurologic examination results (absence of quadriparesis/quadriplegia), increased vascularity of the mass, and anatomically difficult location of the mass. Epidural blood patch, another recommended therapy of intracranial hypotension, was not performed in the patient because of the location of the mass and presence of low-lying tonsils.

Technical aspects of cervical epidural steroid injections may affect outcomes and complications. The cervical epidural space is only a potential space that becomes diminished with pathology such as a protruding disc.[8,9] In this particular case, it is likely that the needle was advanced too far into the right anterior epidural space, producing right-sided nerve root irritation and subsequent dural puncture. Measures to minimize technical complications include using the prone position, advancing the needle with constant fluoroscopic guidance in a lateral view, aiming the needle toward the site of pathology, and using a smaller-gauge (22-gauge) needle. Finally, if the patient experiences severe paresthesia or there is any indication that the dura has been punctured, the practitioner should abort the procedure to avoid injecting steroid into the subarachnoid space or nerve root. CESI should probably be avoided at the level of a large protruding disc and should be performed at another level.

In summary, we describe the case of a 39-yr-old woman who presented with a new-onset herniated disc at C6–C7. She underwent a series of three CESIs with triamcinolone over a 6-week period. Early on, she experienced headaches, night sweats, and upper neck pain. Subsequent cervical MRI revealed a gadolinium-enhancing mass occupying the anterior epidural space. Seven months after the third epidural injection, the headache become incapacitating when the patient was upright. Brain MRI revealed intracranial hypotension. A computed tomographic myelogram showed a CSF leak at C6 on the right. Anterior cervical discectomy and fibrin glue blood patch were performed, with good neurologic outcome.

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Methemoglobinemia after a Blast Injury

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2,4,6-TRINITROTOLUENE (TNT) is used extensively in the manufacturing of explosives. Methemoglobinemia induced by TNT has been previously reported after occupational exposure to TNT in mining and chemical industries.[1,2] However, this is the first report describing the occurrence of methemoglobinemia in a man who was exposed to a blast injury while manipulating a TNT bomb.

Case Report

A 17-yr-old man, previously healthy, sustained a blast injury while manipulating a bomb. Based on information from the patient, the bomb was identified as containing TNT. In the emergency room, the patient was conscious and anxious and reported severe headache. He presented with partial-thickness and full-thickness burns with tattooing on his trunk, upper extremities, and face. Also, he had swollen lips and bilateral severe corneal burns and lacerations. The electrocardiogram, chest radiograph, blood count, coagulation profile, and serum biochemistry results were normal. A fiberoptic bronchoscopy performed under sedation with 2 mg intravenous midazolam revealed normal airways. The patient was scheduled for bilateral corneal suturing and was premedicated with 0.5 mg intramuscular atropine. In the operating room, the patient's heart rate was 90 beats/min, and his blood pressure was 100/70 mmHg. Pulse oximetry (Spo_2) on room air was 89%. The patient was preoxygenated with 100% oxygen using a tight-fitting facemask; however, preoxygenation failed to increase the Spo_2. It was difficult to notice whether the patient's fingers or lips were blue because of the burns and soot due to the explosion. Checking the Spo_2 on the toe revealed cyanosis associated with the same Spo_2 value of 89%. An arterial blood gas analysis (Stat profile 1; Nova Biomedical, Waltham, MA) after the patient had breathed room air for 10 min revealed chocolate-colored blood associated with an arterial partial pressure of oxygen (Pao_2) of 90 mmHg, a partial pressure of carbon dioxide (Pco_2) of 44 mmHg, a pH of 7.35, and an arterial oxygen saturation (Sao_2) of 97%. Arterial blood sampling, repeated after the patient breathed 100% oxygen, showed a significant increase in Pao_2 up to 480 mmHg associated with an Sao_2 of 100%, without any increase in Spo_2 (90%). Methemoglobinemia was suspected because of the low pulse oximetry value associated with a normal Pao_2. However, methemoglobinemia could not be confirmed immediately because of the unavailability of cooximetry. Because it was urgent to repair the corneal lacerations, it was decided to proceed with the surgery as planned. Anesthesia was induced intravenously with 2 mg/kg propofol, 6 mg vecuronium, and 100 μg fentanyl. After tracheal intubation, anesthesia was maintained with 1–2% sevoflurane in 100% oxygen. At the end of surgery, the patient was kept intubated and was ventilated postoperatively with an inspired oxygen fraction (FIo_2) of 40%. The next day, the Spo_2 was 91%, and the diagnosis of methemoglobinemia was confirmed by an arterial blood gas analysis, measured by cooximetry (ABL 700 series; Radiometer, Copenhagen, Denmark), which revealed the following results: Pao_2, 160 mmHg; oxyhemoglobin (O_2Hb) saturation, 98%; reduced hemoglobin (RHb) saturation, 2.2%; carboxyhemoglobin (COHb) saturation, 0.2%; methemoglobin (MetHb) saturation, 18%; functional oxygen saturation, 98% [$Sao_2 = (O_2Hb/O_2Hb + RHb) \times 100\%$)]; fractional oxygen saturation, 80% [$SfO_2 = (O_2Hb/O_2Hb + RHb + COHb + MetHb) \times 100\%$]. No treatment was instituted, and the trachea was extubated uneventfully. On day 3, the Spo_2 during spontaneous breathing of room air increased up to 98%, and analysis of arterial blood gas by cooximetry revealed an Sao_2 of 98%, a Pao_2 of 100 mmHg, an oxyhemoglobin concentration of 96%, and a methemoglobin concentration of 1.8%. The patient was discharged from the hospital on day 4.

Discussion

Acute methemoglobinemia can be hereditary,[3,4] but most often, it is acquired after exposure to a variety of chemicals and drugs,[5] among which nitrites and aniline derivatives have been reported to be the most common agents.[6,7] There were no hereditary factors that might have predisposed our patient to greater methemoglobin formation from TNT exposure.

2,4,6-Trinitrotoluene is a nitroaromatic compound that is used as an explosive in military armaments and as a chemical intermediate in the manufacture of dyestuffs and photographic chemicals.[1] TNT produces methemoglobinemia by a direct oxidizing effect on the hemoglobin.[8] The rate constants of oxyhemoglobin oxidation by nitroaromatic explosives are related to their structure; the rate constant is increased with an increase in a single-electron reduction potential or with a decrease of the enthalpies of single-electron reduction of nitroaromatics.[8] When comparing the structure–activity relations in methemoglobin formation in human erythrocytes by high explosives, 2,4,6-TNT, 2,4,6-tetryl, and 2,4,6-pentryl, 2,4,6-TNT is found to be a more efficient methemoglobin-forming agent than the other explosives.[8] TNT is absorbed through the gastrointestinal tract, the skin, and the lungs.[1] In our patient, inhalation and/or cutaneous absorption are assumed to be the primary pathways for exposure. However, the absence of airway involvement, as evidenced by fiberoptic bronchoscopy, suggests that cutaneous absorption is more likely.

The toxicity of TNT occurs predominantly after occupational exposure in mine workers and chemical indus-

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trial workers.[1,2,9] Also, TNT has been found in the soil, surface water, and groundwater due to the release of waste water from TNT-manufacturing facilities and from buried ammunition wastes.[10,11] Thus, TNT toxicity may occur in individuals drinking contaminated water or ingesting contaminated foods from contaminated soils.[12] In addition to methemoglobinemia, short-term exposure to TNT may result in contact burns to the skin and eyes, headache, weakness, dizziness, nausea, shortness of breath, and tachycardia.[1]

In our patient, who had a methemoglobin concentration of 18%, the oxygen saturation on room air as measured by pulse oximetry was 91%. The absorbance characteristics of methemoglobin are such that the pulse oximetry shows an Spo_2 around 85%, regardless of the Pao_2.[13] The diagnostic test of choice for methemoglobinemia is cooximetry, which provides a spectrophotometric analysis of different hemoglobin types.[14]

In patients with methemoglobinemia, cyanosis is usually observed at concentrations that are greater than 1.5 g/dl and is often one of the earliest clinically evident features of methemoglobinemia.[15] Our patient presented only with cyanosis, with no other symptoms of methemoglobinemia. However, the classic slate-gray cyanosis of the hands and face was masked by burns until further examination revealed cyanosed toes.

In patients with consequences of increased methemoglobin, the decision to treat is based on the methemoglobin concentration as well as on the clinical presentation. Typically, methylene blue is the treatment of choice; it is initiated at methemoglobin concentrations between 10 and 30% in symptomatic patients and in patients with concomitant disease states. In acquired methemoglobinemia, after exposure to the offending agent ends, methemoglobin concentrations usually return to normal within 36 h.[15] Our patient was previously healthy and presented only with cyanosis; hence, no treatment was instituted. His methemoglobin concentration was 18% at 12 h after the exposure and decreased to a concentration of 1.8% after 48 h.

In conclusion, the current report directs our attention to the possibility of developing methemoglobinemia as one of the consequences of TNT explosion.

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