Near-Infrared Spectroscopy Monitored Cerebral Venous Thrombolysis

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ABSTRACT: ***Background:*** Cerebral venous thrombosis is a clinical entity which is readily diagnosed with the advent of modern imaging techniques. Anticoagulation is now a standard therapy, but more recent treatment strategies have included endovascular thrombolysis. While the endpoint of this intervention both clinically and radiographically has not been defined, noninvasive monitoring techniques may add further objective measures of treatment response. ***Clinical Presentation:*** We present a patient with a four day history of worsening headache and papilledema on exam. Superior sagittal, straight, and bilateral transverse sinus thromboses were identified on computed tomography and angiography. ***Intervention:*** Emergent endovascular thrombolysis by a transvenous approach re-established venous patency and resulted in immediate resolution of the patient's symptoms. Cerebral oximetry by near-infrared spectroscopy was utilized during the procedure, and changes in chromophore concentrations correlated directly with angiographic and clinical resolution of the thrombosis. ***Conclusion:*** Near-infrared spectroscopy can provide continuous feedback during thrombolytic therapy in cerebral venous thrombosis and may help define endpoints of such intervention.

RÉSUMÉ: À propos d'un cas de thrombolyse veineuse cérébrale effectuée sous surveillance spectroscopique de proche infrarouge. ***Introduction:*** La thrombose veineuse cérébrale est une entité clinique dont le diagnostic est facile depuis l'avènement des techniques modernes d'imagerie. L'anticoagulation est maintenant le traitement standard, mais il existe des stratégies de traitement plus récentes, dont la thrombolyse endovasculaire. Bien qu'au point de vue clinique ou radiologique les critères de succès de cette intervention n'aient pas été définis, les techniques non invasives de suivi peuvent fournir des mesures objectives de la réponse au traitement. ***Présentation clinique:*** Nous présentons le cas d'une patiente qui s'est présentée avec une histoire de céphalée de plus en plus sévère depuis quatre jours et un oedème papillaire. Des thromboses du sinus longitudinal supérieur, du sinus droit et des sinus latéraux ont été identifiées à la tomodensitométrie et à l'angiographie. ***Intervention:*** Une thrombolyse endovasculaire d'urgence par voie endoveineuse a réétabli la perméabilité veineuse et amené une résolution immédiate des symptômes. L'oxymétrie cérébrale par spectroscopie de proche infrarouge a été utilisée pendant l'intervention et les changements de concentrations chromophores étaient en corrélation directe avec la résolution angiographique et clinique de la thrombose. ***Conclusion:*** Dans la thrombose veineuse cérébrale, la spectroscopie de proche infrarouge peut fournir des informations continues pendant la thrombolyse et peut aider à définir les critères de succès de telles interventions.

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Cerebral venous thrombosis (CVT) is a clinical entity that is being more commonly diagnosed with the advent of modern imaging techniques.[1] The traditionally described spectrum of symptoms resulting from CVT includes headache, papilledema, seizures, and focal deficits, which may progress to coma and death.[2-5] Hemorrhagic venous infarction is common. Early reports of mortality from CVT range from 30-50%.[2,3,5] With the advent of early diagnostic techniques and rapid initiation of therapy, the more recent mortality rates range from 5.5-30%.[6-9] Long term follow-up of patients with no neurologic sequelea is now common.[10] Anticoagulation, which is controversial in the setting of concomittant hemorrhagic infarction, is a standard therapy.[6,11,12] The duration of anticoagulant therapy is usually addressed on a case by case basis. More recent treatment strategies have included systemic thrombolytics, endovascular thrombolysis, and surgical thrombectomy.[13-19]

We present a patient with a four day history of worsening headache secondary to superior sagittal, straight, and bilateral transverse sinus thrombosis, which was associated with a factor V Leiden mutation.[20] She underwent emergent endovascular thrombolysis which re-established venous patency and resulted in immediate resolution of her symptoms. Cerebral oximetry by near-infrared spectroscopy (NIRS) was utilized during the endovascular procedure. Changes in chromophore concentrations correlated directly with the angiographic resolution of the thrombosis and the immediate symptomatic relief.

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CASE REPORT

A 35-year-old white female presented with a symptom complex consistent with superior sagittal sinus thrombosis. She had been previously well with no history of prior venous thrombosis, bleeding diathesis, recent infection, pregnancy, or head injury. There was no prior history or family history of hypercoagulable state. Her symptoms began four days prior to admission with an insidious onset of generalized headache which progressively worsened. There was associated photophobia, and neck stiffness, but no nausea or emesis. Initial systemic blood pressure was 190/110 mmHg. On examination the patient was mildly somnolent, but easily arousable and was oriented to person, place, and time. She had no focal neurologic deficits, but fundoscopy revealed papilledema.

A non-contrast cranial CT scan was obtained at a community emergency department and demonstrated no focal mass effect, and a lumbar puncture was then performed. The opening pressure was not recorded. There were 20 RBCs/mm in the first tube and 16 RBCs/mm in the fourth, 3 WBCs/mm, glucose of 71 mg/dl, and protein of 48 mg/dl. There was no xanthochromia. Routine chemistry studies revealed a sodium of 132 meq/l but other electrolytes were within normal limits. Hematologic studies showed a peripheral WBC of 15,700 with 80% neutrophils, 3% bands and, HCT of 45%. PT, PTT, and PLT studies were within normal limits.

The patient was transferred and evaluated by the neurosurgery service. Review of the CT scan demonstrated a hyperdensity in the superior sagittal sinus indicating thrombosis (Figure 1). Because of the diagnostic CT scan and clinical evidence of symptomatic intracranial hypertension, no magnetic resonnace imaging was performed. Instead, immediate angiography was performed, with plans for endovascular thrombolysis.

A 5 French cerebral catheter was passed into the right jugular vein using fluoroscopic and roadmapping guidance. The jugular bulb was identified with the use of contrast injection and there was a filling defect which was later confirmed to be the inferior aspect of the thrombus. A microcatheter was then used to probe the sinus system. The microcatheter was advanced into the right transverse sinus and venography demonstrated contrast stasis in both transverse sinuses (Figure 2). The catheter was advanced to the torcula where a urokinase (UK) infusion was begun (5,000 units per cc). An intravenous heparin bolus of 5,000 units was also administered at this point in the case followed by a 1,000 unit per hour continuous infusion for the remaining portion of the case. After 250,000 units of UK had been infused, flow was re-established in the left transverse sinus (Figure 3). With gentle manipulation the microcatheter was then directed into the superior sagittal sinus. Venography again demonstrated minimal flow with numerous filling defects that presumably were thrombus (Figure 4). An additional 450,000 units of UK was infused and flow through the superior sagittal sinus was then observed despite the presence of residual thrombus (Figure 5). At this time the patient had almost complete resolution of her headache which had been severe prior to the endovascular procedure. The microcatheter was repositioned in the straight sinus and venography demonstrated slow flow. An additional 600,000 units of UK re-established flow in this region. The catheter was withdrawn to the torcula where venography was again performed and revealed poor flow. Patency was again established with 600,000 additional units of UK. The procedure was terminated.

Cerebral oximetry by NIRS was employed during the endovascular procedure in addition to standard clinical monitoring. A 5 mm diameter near-infrared optode and 5 mm diameter receiving optodes were placed 4 cm apart on the right parietal cortex in the anterior-posterior direction approximately 3 cm from midline. The pathlength was set at the recommended 6 cm and the sampling rate at 5 seconds. The output of the NIRO 500 was collected from the RS232 port into a 386 PC into a serial port via a Software Wedge program (T.A.L. Enterprises, Philadelphia, PA). Continuous cerebral oximetry recording during thrombolysis is found in Figure 6. Concentrations of oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), and total hemoglobin (THb) were high as cerebral venography commenced, and corresponded to low cytochrome oxidase (Cytox) concentrations. These abnormal levels had developed following initial placement of the optodes, while the patient remained stable but drowsy. Successful thrombolysis was associated with a steady normal-

__Figure 1:__ Non-contrasted CT scan demonstrating a hyperdensity in the superior sagittal sinus consistent with thrombosis.

__Figure 2:__ AP view demonstrating the microcatheter in the right transverse sinus with stasis in both transverse sinuses.

__Figure 3:__ AP view demonstrating the microcatheter at the torcula with flow re-established in the left transverse sinus.

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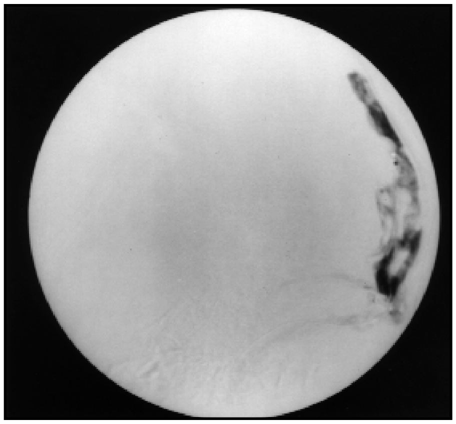

Figure 4: *Lateral view microcatheter in the superior sagittal sinus with numerous filling defects.*

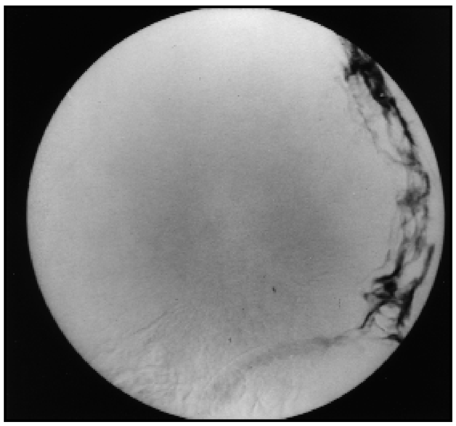

Figure 5: *Lateral view with the microcatheter in the superior sagittal sinus now with flow established despite residual thrombus.*

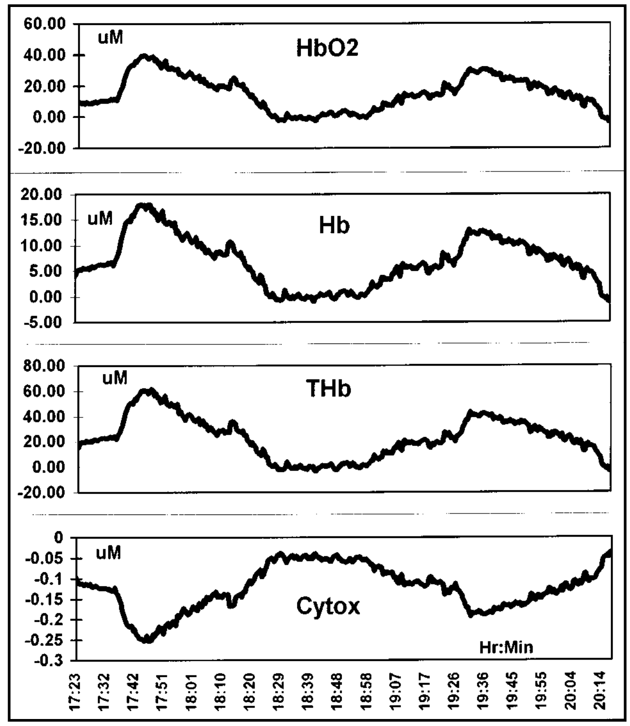

Figure 6: *Graph depicting μM concentrations of chromophores (Y axis) versus time (x axis) as recorded by NIRS during endovascular thrombolysis of the cerebral venous system. Urokinase infusion was initiated at 17:48, at the torcula and superior sagittal sinus with successful re-establishment of flow in the left transverse sinus, torcula, and superior sagittal sinus. Venography revealed poor flow in the straight sinus and again at the torcula. At 19:19, urokinase was re-infused in the straight sinus and then torcula to again establish venous patency. Varying concentrations of cytochrome oxidase (Cytox), oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb) and total hemoglobin (THb) paralleled establishment of venous sinus patency.*

ization of Hb, HbO_2, THb, and Cytox relationships, reflecting reduced cerebral blood volume. Chromophore changes correlated with improved angiographic flow and symptom resolution. All chromophore concentrations, however, increased again, coincident to the finding of torcular re-occlusion. Successful thrombolysis again correlated with a progressive decrease in all chromophore concentrations and a reoxidation of Cytox back to normal levels. Clinical improvement mirrored the radiographic changes and chromophore changes observed with NIRS.

The patient made an excellent recovery and suffered no neurological deficits. She was continued on intravenous, and later, oral anticoagulation. Follow-up imaging demonstrated no evidence of hemorrhage or infarction. Hematologic evaluation revealed a Factor V Leiden mutation, a known risk factor for venous thromboembolism.[21-23] Follow-up MRI performed 6 months from the time of initial presentation showed no residual or new thrombosis. Coumadin was then discontinued.

Discussion

Direct endovascular thrombolysis was performed in the presented case because the patient had extensive CVT producing intracranial hypertension manifesting with drowsiness and papilledema. The correlation of NIRS with successful endovascular thrombolysis and the corresponding clinical improvement were dramatic. Resolution of the CVT in our patient was documented with three lines of observation. First angiographic resolution of clot was observed during urokinase infusion. Second, the patient immediately expressed dramatic symptomatic relief at the same time; specifically, cessation of a generalized headache. Finally, the changes in NIRS chromophore concentrations followed in a very close temporal sequence.

After the first report by Jobsis[24] demonstrating the feasibility of using near-infrared spectroscopy (NIRS) for cerebral oximetry, the technique has undergone considerable development.[25] Specifically, with regard to the NIRO 500 (Hamamatsu Photonics KK) it is now possible to quantify changes in tissue oxygenation on the basis of measurements of oxyhemoglobin (HbO_2), deoxyhemoglobin (Hb), total hemoglobin (THb), and cytochrome oxidase (Cytox) redox state noninvasively through the cranium of neonates[26-29] and adults.[30-34]

This case demonstrates the potential utility of cerebral oximetry by NIRS to provide continuous feedback during thrombolytic therapy in cerebral venous thrombosis (CVT) and the potential application in thrombotic stroke. An ability to monitor the resolution of the thrombosis and perfusion continuously may direct the endovascular interventionalist and help reduce the risks of reperfusion injury, edema, and hemorrhage. NIRS may allow for continuous appreciation of the extent to which the thrombus is being resolved without the neccessity of repeated dye injections to follow the success of thrombolytic therapy. NIRS may also be useful to monitor for evidence of re-thrombosis. Development of hemorrhage or infarct may also be detected in the post procedure period.[35,36]

The endpoint for thrombolytic therapy in the treatment of CVT is not clear.[18] Some reports have utilized infusions for many days in order to have a "normal" angiogram.[19] Others have relied on re-establishment of fluoroscopic flow even if some thrombus remains.[1] Further experience with NIRS during endovascular thrombolytic procedures, arterial or venous, may provide another valuable measure of therapeutic benefit and thereby serve as a marker to direct treatment and its endpoint.

The patient described was found to have activated protein C resistance due to a factor V Leiden mutation. Inheritance of a factor V Leiden mutation is autosomal dominant.[26,43] Activated protein C resistance (APC-R) is a reported risk factor for venous thromboembolism including CVT.[21-23,37-42] Those patients with concomittant APC-R and oral contraceptive use have a 30-50 fold increase in the risk of thrombosis.[43] In our patient a factor V Leiden mutation leading to APC-R was felt to be the primary etiologic factor in her development of CVT. There is no concensus regarding the appropriate duration of anticoagulant therapy. In the absence of prior thrombotic events, we elected to discontinue the coumadin after six months. MRI had confirmed normal cerebral venous patency.

The subject of this study presented with a four day history of progressive headache with no focal neurologic deficit. Diagnostic evaluation revealed diffuse cerebral sinus thrombosis. Successful endovascular thrombolysis using urokinase was performed and the patient made an excellent recovery. Near-infrared spectroscopy was utilized at the time of thrombolysis and chromophore changes directly correlated with symptomatic relief and re-establishment of venous patency as angiographically defined. We feel that CVT represents a clinical scenario in which cerebral oximetry may have clinical application. Tissue oximetry by NIRS is a clinical technique enabling direct, noninvasive, and continuous monitoring of the adequacy of cerebral tissue oxygenation. This technology is now ready for verification of efficacy in a variety of clinical applications.

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