Contrast-Induced Encephalopathy after Cerebral Angiogram: A Case Series and Review of Literature

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Abstract
Contrast-induced encephalopathy (CIE) is a rare complication that arises from exposure to iodinated contrast medium and can result in a range of symptoms, including cortical blindness, aphasia, focal neurological deficits, and altered mental status. We present 4 individual cases of CIE who presented with stroke-mimic symptoms following surgery with localized iodixanol or ioversol injection. We outline a clinical timeline of all patients, showing that CIE follows a general pattern of delayed onset, worsening symptomology, and ultimately full recovery. All patients received IV hydration, corticosteroids, or both as part of their treatment protocol.

Introduction
Contrast-induced encephalopathy (CIE) is a rare presentation of acute neurological disturbances following the administration of iodinated contrast. Symptomology of CIE includes transient cortical blindness, aphasia, focal neurological defects, and altered mentation [1–3]. Although pathophysiology and potential risk factors leading to CIE remain unclear, it is suspected that temporary disruption of the blood-brain barrier integrity leads to the neurotoxic effects seen with CIE [1]. Potential risk factors for CIE include hypertension, diabetes mellitus, renal impairment, administration of large volumes of iodinated contrast, percutaneous coronary intervention, selective angiography of internal mammary grafts, and previous adverse reaction to iodinated contrast [4]. Most cases of CIE are self-limiting and resolve.
spontaneously. Treatment modalities have revolved around the use of corticosteroids, mannitol, or hydration [1]. This article discusses 4 patients with CIE who presented with focal neurological deficits following a diagnostic cerebral angiogram (DCA). All patients received a localized injection of either iodixanol or ioversol, which are both nonionic low osmolar contrast agents. Additionally, we provide a clinical timeline that includes each patients’ symptoms up until their full recovery (shown in Fig. 1).

Case Presentations

Case 1

A 75-year-old woman was treated for an incidentally discovered unruptured anterior communicating artery (ACoA) aneurysm using an intravascular Woven EndoBridge device. Her past medical history included hypertension, dyslipidemia, trigeminal neuralgia, and...
radiation-treated left cerebellopontine angle meningioma 18 years before. The patient was placed under general anesthesia, and the DCA was performed using 98 mL of iodixanol. Post-procedure computed tomography (CT) showed no bleeding, and proper positioning of the device was verified. The patient had no neurological complaints following the procedure and was discharged shortly afterward.

Six hours after surgery, the family noticed that she patient appeared disoriented with an unsteady gait, fatigue, and coordination problems. Two hours later, the patient was unable to recall her name and displayed right-sided facial droop, hemiparesis, and aphasia. Upon arrival at the emergency department, head CT and CT angiogram were negative for any acute ischemia and large-vessel occlusion, and she received tissue plasminogen activator (tPA) for a suspected ischemic stroke. She was admitted to the intensive care unit for observation and medical management. The next day, the patient remained lethargic, aphasic, and hemiplegic with a National Institutes of Health Stroke Scale (NIHSS) of 15, despite being hemodynamically stable. MRI of the brain with and without contrast did not demonstrate any findings consistent with an acute stroke. The most likely diagnosis was CIE. The patient was placed on dexamethasone, dual antiplatelet therapy with aspirin and clopidogrel for stroke prevention, and levetiracetam for seizure prophylaxis. On day 3, she was unable to follow any commands and had right-sided neglect. She developed a fever of 38.2°C, was unresponsive to tactile stimuli, and motor strength was 0/5 in all 4 extremities. Later on day 3, she became hypoxic and chest auscultation revealed wheezing and rhonchi. On days 4 and 5, she showed minor improvements in her condition. By day 6, the patient was more alert, able to follow commands in all extremities, and had improved muscle strength on her right side. On day 7, the patient still had minor confusion, but her weakness improved, her acute hypoxia resolved, and she was discharged to a senior living facility. Any residual word-finding difficulties were resolved later that evening. At her 1-year follow-up, she had returned to her baseline function and offered no additional complaints.

**Case 2**

A 67-year-old woman underwent vessel reconstruction using a Pipeline flex embolization device for a dysplastic left internal carotid artery (LICA) and proximal large LICA aneurysm. Her past medical history is significant for osteoporosis, nephrolithiasis, pulmonary embolism, and postsurgical hypothyroidism. The patient also screened positive for the compound heterozygous MTHFR mutation C677T/A1298C. She was given a total of 62 mL of iodixanol during the procedure. The patient was neurologically intact following the surgery, and there were no complications during this procedure. Three-dimensional rotational angiographic acquisitions with Dyna CTA showed normal anatomy of the left common carotid artery, intercerebral artery, and middle cerebral artery (MCA) and no evidence of stenosis, dissection, aneurysms, or shunting. Postoperatively, the patient maintained stable vital signs and normal urinary function.

Approximately 2 h after surgical completion, the provider noticed the first signs of expressive aphasia as the patient was unable to recall the place, time, and last name. Three hours later, the patient experienced further deterioration in mental status and remained inattentive. The patient was started on intravenous fluids and underwent a DCA which revealed no abnormal findings. Later that evening, the patient remained unable to follow commands and had blood-tinged emesis consisting of blood clots. Shortly thereafter, she remained withdrawn and developed a fever of 38.3°C. She was started on 4 mg of dexamethasone for a presumed diagnosis of CIE. The following morning, the patient’s mental status and speech were greatly improved, and she was discharged. One week after discharge, the patient had symptoms of dizziness and balance which were present prior to surgery in addition to minor memory issues. The follow-up MR imaging was negative for any areas of new stroke or
encephalomalacia. One year later, the patient underwent a similar procedure for the treatment of a second intercerebral artery aneurysm using flow diversion. Prior to the operation, the patient received 4 mg of IV dexamethasone prior to the start of the procedure to avoid potential contrast-induced complications. No postsurgical CIE complications were observed following this intervention.

**Case 3**
A 68-year-old woman presented to the hospital for a DCA with intent to treat a small ACoA aneurysm. Her past medical history included hypertension, hepatitis C, tobacco use disorder, multiple cerebral aneurysms, and a right internal carotid artery thrombectomy. The larger of 2 ACoA aneurysms had been treated with a Woven EndoBridge device 6 months before this admission. The second smaller ACoA aneurysm was visualized and managed by endovascular strategy with coil embolization. Control angiograms were performed after each coil deployment to confirm satisfactory positioning and no parent vessel occlusion, thrombus, or dissection. A total of 148 mL of ioversol was used during the procedure, and the patient was neurologically intact afterward.

Approximately 2 h after the procedure, the patient’s daughter alerted the nurses stating that her mother was “not making any sense.” The patient was noted to be mumbling to herself and disoriented. Her pupils were equal and reactive, and upper and lower extremity motor strength was unchanged. A CT scan was ordered but showed no evidence of acute intracranial hemorrhage or mass effect that would explain her change in the level of consciousness. Dexamethasone and intravenous hydration were initiated based on the suspicion for CIE. After about 2 hours, the patient experienced memory problems, and later in the evening, she became drowsy, weak, and disoriented to person, place, and time. On the following day, the patient remained confused and drowsy and was oriented to person and place only. By hospital day 3 afternoon, she recovered fully to baseline and was discharged on a 2-week tapering course of dexamethasone. The patient and family expressed no further complaints at subsequent encounters. Follow-up imaging including CTH and MR were negative for any new stroke. At her 3-month follow-up DCA, she was premedicated with a 1-day course of prednisone and diphenhydramine for CIE prophylaxis and underwent the procedure uneventfully.

**Case 4**
A 53-year-old woman had a stage I embolization performed on the left distal MCA feeder using an adhesive liquid embolic agent. The operative diagnosis was a left parietal S-M grade 3 AVM with 4-cm nidus and deep venous drainage into the straight sinus and feeders from left dACA, MCA, and PCA. A total of 118 mL of ioversol was used during the procedure. No evidence of stenosis, dissection, or hemorrhage was reported postoperatively; however, the patient experienced transient dysphasia which was a complication of the procedure.

Three hours later, she complained of a periorbital headache which was managed with analgesics and fluids. On the following morning, the patient vomited, and her dysphasia worsened. The next day, the patient had 2 seizure-like events 2 h apart which were subsequently treated with levetiracetam. A CTH without contrast performed 2 days after the event did not reveal any acute ischemia, changes to AVM, or embolization material. The care plan for the patient involved supportive care and continued monitoring for seizure-like activity. On day 4 of hospitalization, the patient’s neurological deficits improved, and she was more alert and later discharged home.

One day after discharge, the patient showed improvement but still complained of headaches. During her 1-week follow-up, the patient localized the headache to the left temporal area with radiation to the back of her head. Ibuprofen, acetaminophen, and fluids did not
completely resolve the pain, and she is seeking further management for the AVM and chronic headaches. The follow-up MR imaging was negative for any areas of new stroke or encephalomalacia.

Discussion

CIE is a rare complication of iodinated contrast that can present with a variety of neurological manifestations. All patients in this study initially presented with confusion, expressive aphasia, or drowsiness that eventually progressed to nausea, vomiting, dizziness, and seizures before completely resolving, which is consistent with previously reported cases of CIE. The selected cases in Table 1 represent publications within the last 10 years that help illustrate common symptoms and management of CIE. While the cases in our report mimicked stroke symptoms, the timing of symptom onset and clinical progression from deterioration to full recovery demonstrate unique characteristics to transient stroke patients who gradually improve over time. The onset of CIE symptoms occurred an average of 3 and a half hours after the completion of the neurosurgical procedures, and this delay in symptom onset decreases the likelihood of surgical complications being the cause. Clinically, it is important to differentiate between stroke and CIE as the administration of tPA can increase vascular permeability of the blood-brain barrier (BBB). Current metabolic models suggest that tPA activates PDGF-CC, which leads to PDGFR-α signaling on perivascular astrocytes interacting with LRP [5]. tPA administration upregulates this pathway and further disrupts BBB integrity [5]. The patient in case 1 was the only patient to receive tPA for a suspected stroke. This patient received a total of 60.3 mg IV tPA and stayed a total of 140.5 h in the hospital which was more than the average of all patients (64 h). It is reasonable to assume that the administration of tPA may complicate the course of CIE and may even worsen CIE symptomology, further highlighting the importance of differentiating CIE from a stroke. Figure 1 highlights the clinical progression of CIE as seen in all 4 patients. The patients had an average symptom onset of 3.2 h following the completion of their surgeries.

During the clinical course of CIE, some of the patients developed high fevers. The brain parenchyma may have been affected by contrast extravasate as a result of BBB failure from inflammatory reactions [6]. TNF-α, which increases during fever, upregulates TLR 2, leading to depolymerization of actin that disrupts the tight junctions that form the BBB [6]. Further, CIE has been shown to be associated with decreased expression of claudins, superoxide dismutase, and catalase, leading to increased brain microvascular permeability [7]. Both an increase in inflammatory reactants and decrease in antioxidant systems may place patients at risk for CIE. Mutations in MTHFR, as in case 2, are associated with increased inflammatory markers that has been shown to be detrimental to cardiovascular health [8]. However, an association between this mutation and neuro-inflammation has not been extensively studied. In patients who are suspected of CIE, it is important to test for any septic markers and initiate prompt treatment with IV hydration and corticosteroids. All of the patients presented in our study, with an exception of patient 4, received IV hydration and high-dose corticosteroids, and all patients went on to full recovery. Furthermore, the patients in cases 2 and 3 were given prophylactic corticosteroids for additional neurosurgical operations scheduled months following their initial CIE events. Both these patients did not experience any contrast-related complications. This is a finding not stated in any previous literature and may serve as a recommendation for providers who treat patients with a history of CIE.

The patients in our cases obtained a DCA prior to stent administration or embolization procedures. Intra-arterial access was obtained through the placement of a catheter into the superficial femoral artery and, the contrast bolus was administered to a specific angiographic...
Table 1. Cases of CIE reported within the last 10 years

| Agent                        | Symptom                                                                 | Duration                           | Treatment                  |
|------------------------------|-------------------------------------------------------------------------|------------------------------------|----------------------------|
| tPA, no contrast [12]        | Transient cortical blindness; MRI diffuse hyperintensities in the subarachnoid space in a fluid-attenuated inversion recovery sequence | 3 days                             | IV fluids                 |
| 110 mL iopromide [4]         | Respiratory distress, erythema on trunk, drowsiness, confusion, disorientation, complete aphasia, muscle weakness | Leg strength returned in 6 h, speech in 12 hours | IV hydrocortisone 3X daily with IV fluids |
| 120 mL iopromide [4]         | Drowsiness, confusion, disorientation, muscle weakness                  | Within hours                        | IV hydrocortisone 3X daily with IV fluids |
| 150 mL ioversol [1]          | Consciousness disturbance, global aphasia, cortical blindness, right-sided weakness | 2 days                             | IV fluids with normal saline |
| 110 mL iopramidol [13]       | Headache, dizziness, nausea; CT scan 2 days after symptoms started showed diffuse cerebral edema with loss of gray-white differentiation, effacement of cerebral sulci, decrease cerebrospinal fluid | 56 days– died from cerebral edema | Ramosetron and dexamethasone |
| 120 mL iohexol for angiography; 220 mL iopramide for procedure [3] | Complete right hemiparesis, sensory loss, right-sided neglect | 20 days; motor power returned in one year | Dexamethasone and mannitol |
| Iodixanol [2]                | Left hemiparesis, sensory loss, left-sided neglect                      | 6 days                             | IV fluids, dexamethasone, mannitol, anticonvulsant |
| Iohexol [14]                 | Headache, transient cortical blindness, seizure, focal neuro deficits; CT showed slight enhancement of venous sinuses and cerebral arteries | 2 days                             | IV fluids                 |
| Agent | Symptom | Duration | Treatment |
|-------|---------|----------|-----------|
| Iopamidol [15] | Severe headache, agitation, altered mentation, skin hypersensitivity; CT showed an increased density of falx and tentorium; MRI after 48 h showed small-vessel ischemia and age-related changes | Mental status and agitation resolved in 48 h; headache resolved after several days | IV fluids, acetaminophen, NSAIDs |
| Iohexol [16] | Confusion, cortical blindness, seizure | 1 day | IV fluids and sedation medication |
| Analgesia pump with gadolinium via fluoroscopy [17] | Encephalopathy, expressive aphasia, confusion; noncontrast CT showed diffuse hypoattenuation of basal cisterns determined to be residual gadolinium contrast | 6 days | IV fluids |
| 120 mL iohexol [18] | Confusion | 9 days | Supportive care |
| Iopamidol (4 patients), and ioxilan (1 patient), mean dose 220 mL [19] | Hemiparesis, convulsions, blindness, consciousness disturbance, hemiparesis, agnosia, aphasia | Improvement after hemodialysis; recovery after 1 week | Hemodialysis to remove contrast and steroids |

The most common presenting symptoms of CIE include confusion, aphasia, cortical or transient blindness, hemiparesis, disorientation, headache, drowsiness, and seizures. The less common symptoms include muscle weakness, dizziness, nausea, vomiting, sensory loss, neglect, skin abnormalities, and loss of consciousness. Different symptoms appear in bold on the table. Of the cases reported within the last 10 years, most incidences of CIE resolved within 2–3 days.

CIE, contrast-induced encephalopathy; CT, computed tomography; tPA, tissue plasminogen activator.
territory. The lateralization of our patients’ symptoms might have correlated with the localized injection territory of the contrast bolus. To date, CIE has not been associated with patients who underwent whole-brain perfusion angiogram utilized in the diagnosis of diffuse and multifocal diseases, and this warrants further investigation.

The current literature shows a synergistic effect between IV contrast dye and NSAIDs, which leads to decreased renal blood flow allowing for longer systemic exposure times [9]. All patients in our study received general preoperative instructions to stop all NSAIDs, herbal medication, and vitamin E supplements 7 days before their respective procedures. Kidney disease is also a well-established risk factor for the development of CIE, and patients with CKD at high risk for CIE are instructed to discontinue all nephrotoxic drugs before contrast administration [10]. None of our patients had documented CKD or renal impairment. They all went under general anesthesia for their neurosurgical operation.

Our patients’ consistent presentations with other reported cases of CIE. As a diagnosis of exclusion, CT or MRI studies are necessary to rule out embolic, hemorrhagic, and hemodynamic etiologies before making the diagnosis of CIE [1, 4]. However, most cases of CIE do not show any changes in imaging. The patient in case 1 underwent electroencephalogram recording, which showed persistent focal left-hemispheric slowing and right frontal lateralized periodic discharges occurring at a frequency of 0.5–1 Hz. These findings indicate nonspecific acute pathologies that can be metabolic or structural disorders [11]. Other patients did not undergo EEG during their acute episodes. Obtaining additional imaging may be helpful in characterizing the event, but its role in changing clinical decision-making may be inconsequential and lead to unnecessary healthcare costs and burden for patients.

**Conclusion**

CIE is an iatrogenic complication of iodinated contrast exposure that must be distinguished from other acute pathologies in the postoperative setting. The high variability in presentation and progression makes CIE a difficult condition to diagnose, and the current literature suggests that CIE can occur irrespective of the contrast agent administered. Most agree that disruption of the blood-brain barrier plays a crucial role in its pathogenesis, though the exact mechanism of damage remains unclear. Increased susceptibility to CIE is seen in patients with underlying hypertension, renal impairment, and previous contrast-related reactions. Our cases highlight the importance of differentiating CIE from acute stroke and the benefit of prompt corticosteroid administration. Furthermore, patients with a documented history of CIE should receive prophylactic corticosteroid and antihistamine for all subsequent neurosurgical interventions involving iodinated contrast.

**Statement of Ethics**

Informed consent was obtained for participation from all patients reported in this case series. Written informed consent was obtained for publication of this case series and all accompanying images from all patients reported in this case series. A copy of the consents is available for reviewers of this journal.

**Conflict of Interest Statement**

There are no conflicting or competing interests to declare.
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Author Contributions

Dr. Ramin Zand is the corresponding author for this report, and in addition to reviewing the patient’s imaging and contributing to the primary direction of the paper, he is responsible for responding to critiques about the paper after publication. Dr. Clemens Schirmer was responsible for analyzing the patient clinical, diagnostic, and treatment data. Jason Park, Vaibhav Sharma, and Cecelia Allison were responsible for the patient chart reviews and writing the case presentations. Vaibhav Sharma created the clinical timeline for each patient. Cecelia Allison created the table to represent the literature review. She is also the primary author with the responsibility of submitting the case series to the journal. All authors contributed to writing the discussion, editing, and reviewing the paper. All designated authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

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