Cerebral Edema in Disguise: A rarely reported complication of contrast dye
Abstract

Introduction: Over the years, medical imaging has evolved to include the use of contrast dyes to better diagnose pathology. In 2005 alone, the United States did at least 10 million of these diagnostic radiographs\(^1\). These contrast dyes are injected and rapidly distributed, which has raised concerns for adverse events. Because of these concerns, older ionic contrast media have been replaced by non-ionic contrast agents such as iohexol\(^3,4\).

Case Presentation: In this clinical case, we present a 35-year-old female who developed a rare neurologic complication to this favored contrast media. Before the patient’s second visit to the emergency department in one day, the patient had a catheter dye study at her pain management physician’s office, which utilized iohexol to monitor the effectiveness of the patient’s pain pump. The patient was sent to the emergency department because of severe back pain. This progressed to headaches, nausea, vomiting, throat swelling, slurred speech, word finding difficulty, pain with leftward gaze, and seizures. A computed tomography scan of her head suggested cerebral edema. Intravenous mannitol and several antibiotics were given as the patient was transferred to neurological intensive care unit. In the morning, a repeat computed tomography scan showed improved cerebral edema. Magnetic resonance imaging was also done in the morning and was normal. Her symptoms completely resolved and she was discharged two days later.

Conclusion: A few other cases of cerebral edema with non-ionic contrast have been reported and have suggested to not use computed tomography imaging within three days of intrathecal use of iohexol, because it falsely shows increased uptake as cerebral edema. Any changes were transient, as they were in this case\(^14,16,17\). Our case was different from the aforementioned cases because the patient’s symptoms were consistent with a diagnosis of cerebral edema. We mostly agree with the previous conclusion, as long as the patient is not symptomatic. If the patient has symptoms of neurologic changes, interventions such as mannitol may be necessary to prevent long-term changes. We additionally conclude that MRI may be a better scan than CT to detect if there is clinically relevant cerebral edema.
**Introduction**

Medical imaging has utilized contrast dyes for many years. In 2005, this included over 70 million diagnostic radiographic exams each year, at least 10 million of which are in the United States alone\(^1\). For these scans, large amounts of chemically inert dyes are injected intravascularly and rapidly distributed. As a result, there is a concern for adverse events, and therefore the types of commonly used contrast media have changed over time.

Contrast agents are classified based on charge (ionic or nonionic), molecular structure (monomeric or dimeric), and the relative osmolality of injected preparation (high, low, iso-)\(^2\). In the 1950s, the conventional contrast agent was an ionic, monomeric, triiodinated benzoic acid derivative. Since then, in the mid-1980s, low-osmolality contrast agents have gained popularity. This includes nonionic monomers or ionic dimers. However, a study done in 1990 of over 300,000 contrast studies found the overall risk of adverse drug reaction to be 0.2% for ionic contrast media and 0.04% for non-ionic contrast media\(^3\). Cochran *et al* had a similar finding in over 100,000 contrast administrations during 1985-1999, with mild and moderate adverse events more common in ionic compared to nonionic contrast\(^4\).

In this clinical case, we explore the use of iohexol, a nonionic contrast medium, intrathecally in a catheter dye study. This study is similar to myelography. Myelograms are used to evaluate spinal pathology and have a low risk overall of seizures, contrast reactions, or bleeding\(^5\). In the past, cerebral edema was well-documented finding with intrathecal injection of ionic contrast media, but this is a less reported finding with nonionic contrast media. The first nonionic agent, metrizamide, was introduced in 1969 and has also caused hyperdense gray matter and was found to accumulate in sulci\(^6\). Metrizamide has also been linked to seizures and encephalopathy\(^7\). These complications are thought to arise because of osmotic disruption of the blood brain barrier. Newer agents like iohexol and iopamidol in the late 1970s replaced metrizamide with lower risk of adverse neurologic effects\(^8\).

Iohexol has been considered a first-line contrast media for neurological imaging procedures including myelography\(^9\), but there are still adverse effects. These concerns include the common contrast-induced nephropathy or renal failure from lack of hydration before and after the scan. Adverse effects linked with iohexol particularly are hypersensitive allergic reactions, seizures (in those with a history of epilepsy), and thromboembolic events. Disease-related concerns are present for those with epilepsy, severe cardiovascular disease, chronic alcoholism, multiple sclerosis, and old age\(^10\). With myelography, iohexol’s side effects have included headaches, nausea, and vomiting, with no other neurologic abnormalities\(^11\). We will profile a patient without the related disease interactions for iohexol who presented with a rare transient neurologic complication to this favored contrast media.
Case Presentation

A 35-year-old female with a past medical history of chronic back pain, interstitial cystitis, pelvic floor dysfunction, anxiety, and depression presented to the emergency department (ED) with severe back pain. She had a pain pump installed 5 months earlier for chronic low back and pelvic pain. The week before her event, her pump was evaluated in the office and was found to be functioning normally, but she had tenderness around the pump site on exam. In the past, her back pain was localized to a specific spot on her back, but the day after the pump evaluation she developed new “shooting pains” that radiated down her arms and legs. Four days later, she thought the pain was exacerbated when she utilized her bolus device and stopped using it. She presented to an ED close to home for an evaluation of her worsening back pain. The etiology of her pain was not determined, and she left with recommendations to follow up with her pain management physician. At the clinic later that day, a catheter dye study was performed to evaluate the integrity of the system. After aspiration of the catheter, 5ml of iohexol 240mg/ml was injected into the intrathecal space. The physician took a sample of cerebrospinal fluid and also did a scan with dye to check the effectiveness of the pump. The dye study demonstrated a normal functioning system with normal spread of dye throughout the intrathecal space. During the injection however, the patient reported severe back pain. Due to the unknown etiology of the patient’s symptoms, the patient was sent to this ED for further evaluation and care. She denied any recent fever, vision changes, cough, chest pain, or shortness of breath. There were no other complaints.

She has an extensive surgical history including sinus surgery, appendectomy, conization, left shoulder surgery, rhinoplasty, 2 pelvic laparoscopies for endometriosis, spinal cord stimulator, pain pump trial, intrathecal catheter placement, and left buttock pump and catheter implantation most recently. She denied tobacco, alcohol, or recreational drug use. She has been unemployed for a few weeks because she has recently been in a lot of pain. She had no associated family medical history. She denied any sick contacts or travel.

Her pain pump medications include baclofen, bupivacaine, clonidine, and hydromorphone. She started a few medications one week ago: amitriptyline, desipramine, tizanidine, and trazodone. Her home medications include citalopram, flavoxate, flonase, hydroxyzine, loratidine, magnesium, metoclopamide, pentosan polysulfate, tropium, vitamin D3, vitamin B complex, and a probiotic tablet. She has an allergy to pregabalin (swelling) and ketorolac (anaphylaxis). Many food items exacerbate her interstitial cystitis, including tomato, green pepper, cider vinegar, caffeine, black pepper, citric acid, chocolate, and nitrates.

Her vitals included a high blood pressure of 146/99, pulse of 102, respiration rate of 16, temperature of 99.1F, and oxygen saturation of 100% on room air. On physical exam, she had left paracervical, parathoracic, and paralumbar tenderness to palpation. Her intrathecal pump was present in the left buttock and the catheter insertion site was present at L4-L5. She had weakness in the left arm and leg, strength was 2/4 on the left and 4/4 on the right. Sensation was intact, with subjective paresthesias in the left hand. Reflexes were intact. In the ED, magnetic resonance imaging (MRI) was not done because the patient had hair extensions that were incompatible with MRI. Two hours after being seen by the ED physician, she complained of severe headaches as well as nausea and vomiting. The patient later complained of throat swelling and difficulty talking. Her mother noted that the patient’s speech was slurred and she was having ‘trouble finding her words’. She also complained of neck stiffness and difficulty moving her left eye laterally. During the computed tomography (CT) scan of her head, the nurse noticed that the patient had uncontrollable spontaneous contractions of her upper and lower extremities that lasted a few seconds. The patient was fully conscious at the time.
On exam after this episode, she was in mild distress, had generalized edema, and could not lay comfortably on her hospital bed. She stayed in one position, on her right side. She had difficulty maintaining her gaze to the left with her left eye secondary to pain. Her neck was now stiff. Her back was still tender on palpation on the left and she could still move all extremities spontaneously. Significant lab values include mild hypokalemia at 3.3 and a normal white blood cell (WBC) count of 6.3. CT head, compared to the CT head done at a different ED early in the morning at a different hospital, showed new effacement of cerebral sulci and effacement or near effacement of basal cistern suggesting generalized cerebral edema; crowding at foramen magnum; no mass effect; no midline shift (Figure 1). MRI was still unavailable because of the patient’s hair extensions. The need for an MRI was stressed and the patient and family agreed to have the extensions removed.

The cause of the cerebral edema was unclear, and the patient was transferred to the neurological intensive care unit (ICU) at a different hospital for cerebral pressure monitoring. The on-call neurologist recommended empiric intravenous (IV) antibiotics and 1 dose of 50 gram IV mannitol after the antibiotics. She was prophylactically started on vancomycin, cefepime, acyclovir and dexamethasone. She had some seizure-like movements on transfer to the neurological ICU and was also started on Keppra. She was intubated to protect her airway and lower her carbon dioxide levels to help with the cerebral edema.

Electroencephalography (EEG) was performed when the patient appeared lethargic in the neurological ICU. It showed diffuse cerebral slowing, consistent with her cerebral edema. Her transthoracic echocardiogram was negative and only showed a mildly dilated right ventricle with mild hypokinesis. The lumbar puncture was mostly negative; it showed clear fluid, 7 nucleated cells (normal 0-5), protein 67 (normal 15-45), glucose 79 (normal 50-75).

Cerebrospinal fluid (CSF) drawn at the pain clinic was negative for infection. She also had a negative CSF cytology, negative bronchoscopy, and negative right lower lobe bronchial washing. Her WBC count remained negative. A CT brain done in the morning showed improved cerebral edema with interval reappearance of the fourth ventricle, which was previously obliterated (Figure 2). MRI (Figure 3), magnetic resonance angiogram, and magnetic resonance venogram were completed in the morning, and were unremarkable.

The patient had stabilized and was transferred out of the neurological ICU to the medical surgical floor. At this time, her WBC count jumped to 13.8, likely secondary to dexamethasone. Her physical exam included left facial swelling, right upper lip swelling, and slurred speech. Toxicology questioned if cerebral edema was caused by new medications (started 1 week ago) or supplements, but since her CT head 2 days ago at a different hospital was negative, ruled this out.

It was ultimately concluded that the patient’s transient cerebral edema was an adverse reaction to the contrast dye iohexol, which used for a catheter dye study under fluoroscopy at her pain physician’s office just before being sent to the ED for this hospitalization. The patient was instructed to follow-up with a neurologist and her pain physician. On follow-up six months later, the patient’s left sided pain prior to the catheter dye study is slowly improving. Her weakness and strength returned to normal.
Cerebral edema is defined as a pathological increase in the water mass within the brain interstitial space. The swelling causes a mass effect, which exerts pressure on the surrounding tissue, opposed by the rigid enclosure of the skull\textsuperscript{12}. Signs and symptoms of cerebral edema can be abnormal response to pain, headache, vomiting, altered mental status, sustained heart deceleration, lethargy, or decorticate or decerebrate posturing\textsuperscript{13}.

It has been recommended that any necessary diagnostic CT should be performed before or postponed 3 days after myelography. Both utilize intrathecal injections and assess the flow of CSF. This recommendation was made to avoid viewing intracranial contrast-opacification, which may be mistaken for cerebral edema\textsuperscript{14}. After myelography and catheter dye study procedures, contrast is distributed in the subarachnoid space. Distribution is thought to be dependent on two factors: the position of the patient and the flow and diffusion of CSF. The contrast medium reaches the ventricle system directly through lateral and median apertures, or indirectly by the choroid plexus. Attenuation wanes from basal cisterns through fourth, third, and lateral ventricles and contrast is diluted\textsuperscript{15}.

This theory of increased enhancement of contrast media on CT scans that may lead to a misleading diagnosis of cerebral edema has been supported by a few publications. In a study of fourteen patients undergoing cervical myelography, eleven patients showed subcortical enhancement on CT after myelography, which declined during the following hours. Seventy-eight percent of patients had side effects, the most severe of which were headaches, present in two patients. All symptoms were transient and resolved within 24-48 hours. There was a significant deterioration in the verbal paired associates test, similar to our patient’s word finding difficulty, which was absent at retest a week later in the study. They suggested that iohexol is taken up by brain parenchyma and gradually disappeared within 48 hours. This study, however, had no EEG abnormalities or seizures\textsuperscript{16} unlike our patient. A case in 2014 that also used iohexol had a similar conclusion with patient whose only symptom was minimal left nasolabial flattening. Her CT scan showed cerebral edema, which resolved by a following scan the next morning\textsuperscript{17}. This was different from our case, since our patient became fairly symptomatic with headaches, vomiting, slurred speech, limited gaze, and seizures, so the cerebral edema was more than an illusion in our case.

In 2011, a patient showed symptomatic cerebral edema with lumbar myelography using iopimadol, another nonionic, low-osmolar contrast agent. This patient’s symptoms included lethargy and sluggishly reacting pupils bilaterally. The patient’s head CT showed a similar obliteration of basal cisterns and cerebral sulci as our patient. Her hospital course was slower than our patient, because she showed a slower return to baseline and was discharged five days later on a decadron taper\textsuperscript{18}. Our patient had an overnight recovery to baseline and was discharged without any new medications. In both cases, any change in neurologic status came back to baseline.

Of note, there has been a case of a lasting adverse effect from myelography with iohexol. The patient had a nonfluent speech deficit that gradually resolved, but was left with persistent neurogenic stuttering. The initial CT scan showed the expected increased uptake mimicking cerebral edema. MRI showed no abnormal findings seven days later, while the EEG still had sporadic sharp wave activity\textsuperscript{19}.

Additionally, there have been multiple reported cases of reversible symptomatic neurologic changes with cardiac angiography. These include global amnesia\textsuperscript{20}, cortical blindness\textsuperscript{21}, and encephalopathy\textsuperscript{22} in adults. In one case, iopimadol was linked to seizures, no focal neurologic deficit, and brain CT findings of hyperdensity with effacement of sulci. A repeat CT of this patient 24 hours later showed similar
interval improvement of the hyperdensity. This effacement, identified as cerebral edema, can also be mistakenly read as a subarachnoid hemorrhage (SAH) and presents with a challenge\textsuperscript{23, 24}. To differentiate blood from contrast media and rule out SAH, it is vital to use MRI\textsuperscript{25, 26} since treatment of cerebral edema and SAH differ.

Magnetic resonance imaging could also prove to be a more useful study to check for cerebral edema after intrathecal use of nonionic agents, because the increased contrast uptake may not impact the diagnostic impression. It would have been of great utility if a MRI scan were available for this patient while she was symptomatic, but this was not possible until her hair extensions were removed overnight. We cannot clearly correlate this with our case, since our patient was unable to do an MRI until the morning, when her CT showed her cerebral edema subsided. However, the MRI scan (Figure 3) did not show cerebral edema in the morning. On the other hand, the morning CT scan(Figure 2) showed rapidly improved, but still present, cerebral edema.

Unless a patient is symptomatic for cerebral edema and needs urgent treatment, we support the prior conclusion that head CT should not used for diagnosis within 3 days of myelography. In many cases, cerebral edema was diagnosed based on the CT scan, even though the patients were asymptomatic. This case, however, is a rare example of symptomatic cerebral edema. Appropriate decisions were made to administer mannitol to decrease pressure. The increased uptake read as cerebral edema on CT dissipated by the next morning, and symptoms resolved, similar to most other cases with other new nonionic agents. We additionally conclude that MRI may be a better scan than CT to detect if there is clinically relevant cerebral edema.

Awareness of this complication of iohexol is one factor, but prevention and treatment of symptomatic cerebral edema are important as well. In the future, it may be possible to use skin testing to see if a patient will show hypersensitivity to contrast media in the form of anaphylaxis\textsuperscript{27}. The same cannot be said for predicting the likeliness of neurotoxic reactions with contrast media, and this is an area that warrants more research. In terms of treatment for symptoms of increased intracranial pressure in cerebral edema, mannitol is one option, as was used in this case. A non-pharmacologic alternative is to use osteopathic lymphatic techniques, if the patient has an effective lymphatic system. This leads to increased respiration and circulation, encouraged absorption of fluid, and decreased extravasation of proteins into the interstitium\textsuperscript{28}. Techniques such as pedal pump and thoracic pump are examples of these techniques, and they are safe to use to help decrease intracranial pressure and contribute to recovery\textsuperscript{29}.
Abbreviations

ED = Emergency Department, MRI = magnetic resonance imaging, CT = computed tomography, WBC = white blood cell, ICU = intensive care unit, IV = intravenous, EEG = electroencephalography, CSF = cerebrospinal fluid, SAH = subarachnoid hemorrhage

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Disclosures

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References

Figure 1: Computed tomography scan of the head, read as new effacement of cerebral sulci and effacement or near effacement of basal cistern suggesting generalized cerebral edema; crowding at foramen magnum; no mass effect; no midline shift.
Figure 2: Computed tomography scan of the head the next morning, showing improved cerebral edema with interval reappearance of the fourth ventricle.
Figure 3: Magnetic resonance imaging done in the morning hours, which appears unremarkable.