

Delirious after undergoing workup for stroke

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Ms. L, age 91, experiences acute altered mental status after undergoing routine evaluation of an episode of left-sided weakness. What could be causing her symptoms?



How would you handle this case?

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CASE Altered mental status after stroke workup

Ms. L, age 91, is admitted to the hospital for a neurologic evaluation of a recent episode of left-sided weakness that occurred 1 week ago. This left-sided weakness resolved without intervention within 2 hours while at home. This presentation is typical of a transient ischemic attack (TIA). She has a history of hypertension, bradycardia, and pacemaker implantation. On initial evaluation, her memory is intact, and she is able to walk normally. Her score on the St. Louis University Mental Status (SLUMS) exam is 25, which suggests normal cognitive functioning for her academic background. A CT scan of the head reveals a subacute stroke of the right posterior limb of the internal capsule consistent with recent TIA.

Ms. L is admitted for a routine stroke workup and prepares to undergo a CT angiogram (CTA) with the use of the iodinated agent iopamidol (100 mL, 76%) to evaluate patency of cerebral vessels. Her baseline blood urea nitrogen (BUN) and creatinine levels are within normal limits.

A day after undergoing CTA, Ms. L starts mumbling to herself, has unpredictable mood outbursts, and is not oriented to time, place, or person.

Which laboratory and/or imaging tests should Ms. L undergo next?

- repeat BUN and creatinine levels
- urinalysis and comprehensive metabolic profile
- repeat CT scan of the head
- diffusion-weighted MRI
- blood culture for signs of infection

The authors' observations

Due to her acute altered mental status (AMS), Ms. L underwent an emergent CT scan of the head to rule out any acute intracranial hemorrhages or thromboembolic events. The results of this test were negative. Urinalysis, BUN, creatinine, basic chemistry, and complete blood count panels were unrevealing. On a repeat SLUMS exam, Ms. L scored 9, indicating cognitive impairment.

Ms. L also underwent a comprehensive metabolic profile, which excluded any electrolyte abnormalities, or any hepatic or renal causes of AMS. There was no sign of dehydration, acidosis, hypoglycemia, hypoxemia, hypotension, or bradycardia/

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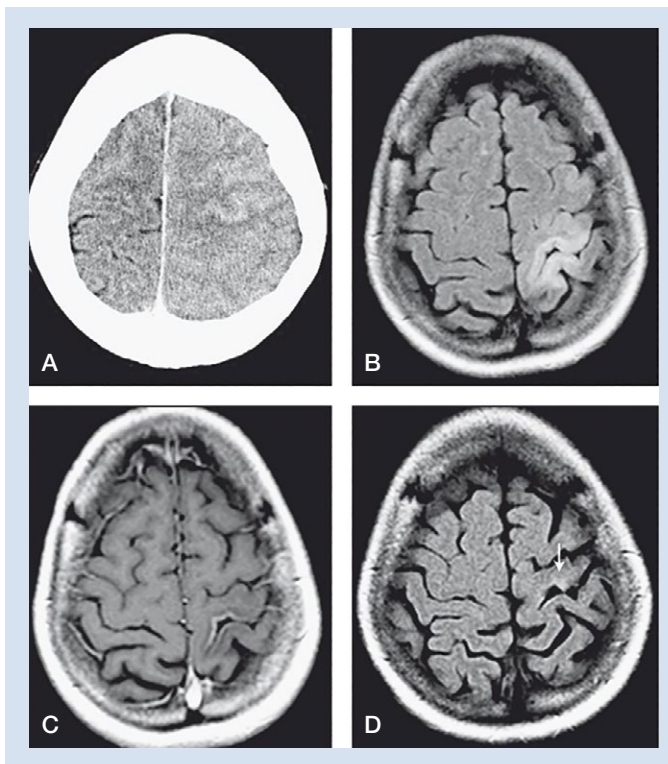
Disclosures

The authors report no financial relationships with any company whose products are mentioned in this article, or with manufacturers of competing products.

Clinical Point

Delayed reactions to contrast agents involve a T-cell mediated response that most commonly results in pruritus and urticaria

Figure 1
Radiologic findings of subarachnoid contrast enhancement



were unable to conduct this test because Ms. L had a pacemaker. Barber et al² suggested that in the setting of acute stroke, the use of MRI may not have an added advantage over the CT scan of the head.

Which of the following is the most likely diagnosis for Ms. L?

- a) post-ictal phenomenon
- b) new-onset ischemic changes
- c) contrast-induced encephalopathy
- d) new-onset hemorrhagic changes
- e) hyperperfusion syndrome

TREATMENT Rapid improvement with supportive therapy

Intravenous fluids are administered as supportive therapy to Ms. L for suspected contrast-induced encephalopathy (CIE). The next day, Ms. L experiences a notable improvement in cognition, beyond that attributed to IV hydration. By 3 days post-contrast injection, her SLUMS score increases to 15. By 72 hours after contrast administration, Ms. L's cognition returns to baseline. She is monitored for 24 hours after returning to baseline cognitive functioning. After observing her to be in no physical or medical distress and at baseline functioning, she is discharged home under the care of her son with outpatient follow-up and rehab services.

tachycardia. A urinalysis, chest X-ray, complete blood count, and 2 blood cultures conducted 24 hours apart did not reveal any signs of infection. There were no recent changes in her medications and she was not taking any sleep medications or other psychiatric medications that might precipitate a withdrawal syndrome.

There have been multiple reports of contrast-induced nephropathy (CIN), which may be evidenced by high BUN-to-creatinine ratios and could cause AMS in geriatric patients. However, CIN was ruled out as a potential cause in our patient because her BUN-to-creatinine was unremarkable.

Routine EEG was clinically inconclusive. Diffusion-weighted MRI may have been helpful to identify ischemic strokes that a CT scan of the head might miss,¹ but we

administered as supportive therapy to Ms. L for suspected contrast-induced encephalopathy (CIE). The next day, Ms. L experiences a notable improvement in cognition, beyond that attributed to IV hydration. By 3 days post-contrast injection, her SLUMS score increases to 15. By 72 hours after contrast administration, Ms. L's cognition returns to baseline. She is monitored for 24 hours after returning to baseline cognitive functioning. After observing her to be in no physical or medical distress and at baseline functioning, she is discharged home under the care of her son with outpatient follow-up and rehab services.

The authors' observations

For Ms. L, the differential diagnosis included post-ictal phenomenon, new-onset ischemic or hemorrhagic changes, hyperperfusion syndrome, and CIE.



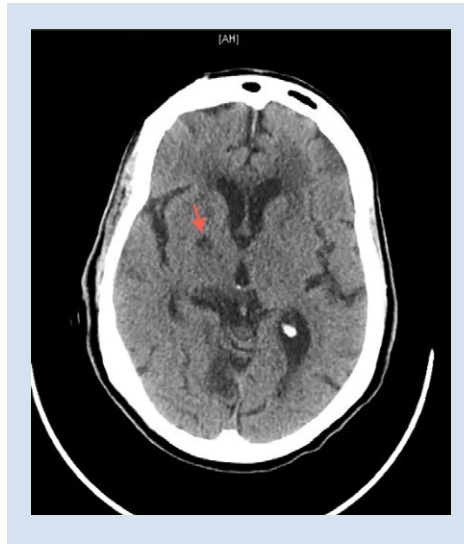
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Seizures were ruled out because EEG was inconclusive, and Ms. L did not have the clinical features one would expect in an ictal episode. Transient ischemic attack is, by definition, an ischemic event with clinical return to baseline within 24 hours. Although a CT scan of the head may not be the most sensitive way to detect early ischemic changes and small ischemic zones, the self-limiting course and complete resolution of Ms. L's symptoms with return to baseline is indicative of a more benign pathology, such as CIE. New hemorrhagic conversions have a dramatic presentation on radiologic studies. Historically, CIE presentations on imaging have been closely associated with the hyperattenuation seen in subarachnoid hemorrhage (SAH). The absence of typical radiologic and clinical findings in our case ruled out SAH.

Typical CT scan findings in CIE include abnormal cortical contrast enhancement and edema, subarachnoid contrast enhancement, and striatal contrast enhancement (*Figure 1 [page 44], Figure 2, and Figure 3 [page 46]*). Since the first clinical description, reports of 39 CT-/MRI-confirmed cases of CIE have been published in English language medical literature, with documented clinical follow-up³ and a median recovery time of 2.5 days. In a case report by Ito et al,⁴ there were no supportive radiographic findings. Ours is the second documented case that showed no radiologic signs of CIE. With a paucity of other etiologic evidence, negative lab tests for other causes of delirium, and the rapid resolution of Ms. L's AMS after providing IV fluids as supportive treatment, a temporal correlation can be deduced, which implicates iodine-based contrast as the inciting factor.

Iodine-based contrast agents have been used since the 1920s. Today, >75 million procedures requiring iodine dyes are performed annually worldwide.⁵ This level of routine iodine contrast usage compels a mention of risk factors and complications from using

Figure 2
CT scan of the head showing prior chronic hypodensity



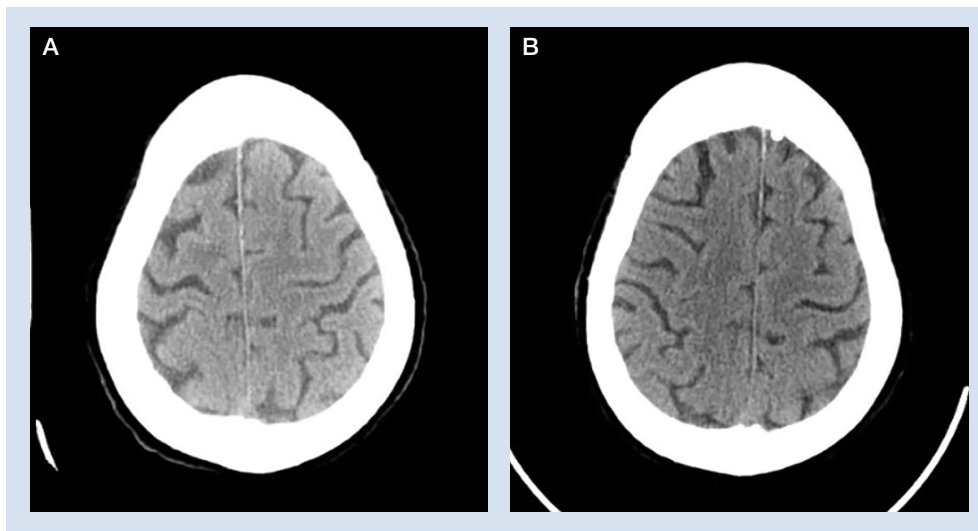
such dyes. As a general rule, contrast agent reactions can be categorized as immediate (<1 day) or delayed (1 to 7 days after contrast administration). Immediate reactions are immunoglobulin E (IgE)-mediated anaphylactic reactions. Delayed reactions involve a T-cell mediated response that ranges from pruritus and urticaria (approximately 70%) to cardiac complications such as cardiovascular shock, arrhythmia, arrest, and Kounis syndrome. Other less prevalent complications include hypotension, bronchospasm, and CIN. Patients with the following factors may be at higher risk for contrast-induced reactions:

- asthma
- cardiac arrhythmias
- central myasthenia gravis
- >70 years of age
- pheochromocytoma
- sickle cell anemia
- hyperthyroidism
- dehydration
- hypotension.

Although some older literature reported correlations between seafood and shellfish allergies and iodine contrast reactions,

Clinical Point

Patients may be at increased risk for contrast reactions if they have asthma, arrhythmias, or hyperthyroidism

Figure 3**CT scan of the head showing lack of contrast enhancement****Clinical Point**

Encephalopathy has been documented after administration of iopromide, iohexol, ioxilan, and metrizamide

more recent reports suggest there may not be a direct correlation, or any correlation at all.^{5,6}

Iodinated CIE is a rare complication of contrast angiography. It was first reported in 1970 as transient cortical blindness after coronary angiography.⁷ Clinical manifestations include encephalopathy evidenced by AMS, affected orientation, and acute psychotic changes, including paranoia and hallucinations, seizures, cortical blindness, and focal neurologic deficits. Neuroimaging has been pivotal in confirming the diagnosis and in excluding thromboembolic and hemorrhagic complications of angiography.⁸

Encephalopathy has been documented after administration of iopromide,^{9,10} iohexol,¹¹ ioxilan,⁴ and metrizamide. The mechanism of neurotoxicity is unclear, but several theories have been formulated. The contrast agent may disturb the blood-brain barrier and enter the brain. This may be a primary mechanism leading to encephalopathy when the hypertonic contrast agent draws water out of the endothelial cells of brain capillaries, arterioles, and venules. This may cause

the endothelial cells to shrink and to separate at tight junctions directly affecting the blood-brain barrier. Alternatively, the increase in intraluminal pressure caused by injection of the contrast agent, in concert with contrast agent-induced cerebral vasodilatation, might contribute to increasing vascular wall tension, further separating tight junctions. A third theory suggests that vesicular transport may be a mechanism of osmotic barrier opening. Further studies would be required to investigate these mechanisms.

Regardless of the mechanism, all the above-mentioned studies note a reversal of radiologic and neurologic findings without any deficits within 48 to 72 hours (median recovery time of 2.5 days).³ All reported cases of CIE, including ours, were found to be completely reversible without any neurologic or radiologic deficits after resolution (48 to 72 hours post-contrast administration).

Clinicians should have a high index of suspicion for CIE in patients with recent iodine-based contrast exposure. From a practical standpoint, such a mechanism could be easily missed because while use of

a single-administration contrast agent may appear in procedure notes or medication administration records, it might not necessarily appear in documentation of currently administered medications. Also, such cases might not always present with unique radiologic findings, as illustrated by Ms. L's case.

References

1. Moreau F, Asdaghi N, Modi J, et al. Magnetic resonance imaging versus computed tomography in transient ischemic attack and minor stroke: the more you see the more you know. *Cerebrovasc Dis Extra*. 2013;3(1):130-136.
2. Barber PA, Hill MD, Eliasziw M, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76(11):1528-1533.
3. Leong S, Fanning NF. Persistent neurological deficit from iodinated contrast encephalopathy following intracranial aneurysm coiling: a case report and review of the literature. *Interv Neuroradiol*. 2012;18(1):33-41.
4. Ito N, Nishio R, Ozuki T, et al. A state of delirium (confusion) following cerebral angiography with ioxilan: a case report. *Nihon Igaku Hoshasen Gakkai Zasshi*. 2002;62(7):370-371.
5. Bottinor W, Polkampally P, Jovin I. Adverse reactions to iodinated contrast media. *Int J Angiol*. 2013;22:149-154.
6. Cohan R. AHRQ Patient Safety Network Reaction to Dye. US Department of Health and Human Services Agency for Healthcare Research and Quality. <https://psnet.ahrq.gov/webmm/case/75/reaction-to-dye>. Published September 2004. Accessed March 5, 2017.

Related Resources

- Donepudi B, Trottier S. A seizure and hemiplegia following contrast exposure: Understanding contrast-induced encephalopathy. *Case Rep Med*. 2018;2018:9278526. doi: 10.1155/2018/9278526.
- Hamra M, Bakhit Y, Khan M, et al. Case report and literature review on contrast-induced encephalopathy. *Future Cardiol*. 2017;13(4):331-335.

Drug Brand Names

iohexol • Omnipaque	iopromide • Ultravist
lopamidol • Isovue-370	loxilan • Oxilan

7. Fischer-Williams M, Gottschalk PG, Browell JN. Transient cortical blindness: an unusual complication of coronary angiography. *Neurology*. 1970;20(4):353-355.
8. Lantos G. Cortical blindness due to osmotic disruption of the blood-brain barrier by angiographic contrast material: CT and MRI studies. *Neurology*. 1989;39(4):567-571.
9. Kocabay G, Karabay CY. Iopromide-induced encephalopathy following coronary angioplasty. *Perfusion*. 2011;26:67-70.
10. Dangas G, Monsein LH, Laureno R, et al. Transient contrast encephalopathy after carotid artery stenting. *Journal of Endovascular Therapy*. 2001;8:111-113.
11. Sawaya RA, Hammoud R, Arnaout SJ, et al. Contrast induced encephalopathy following coronary angioplasty with iohexol. *Southern Medical Journal*. 2007;100(10):1054-1055.

Clinical Point

Clinicians should have a high index of suspicion for CIE in patients with recent iodine-based contrast exposure

Bottom Line

Have a high index of suspicion for contrast-induced encephalopathy, especially in geriatric patients, even in the absence of radiologic findings. A full delirium/dementia workup is warranted to rule out other life-threatening causes of altered mental status. Timely recognition could enable implementation of medication-sparing approaches to the disorder, such as IV fluids and frequent reorientation.