# Clinical Reasoning: A case of acute encephalopathy and rigidity in a 30-year-old man

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## Section 1

A 30-year-old previously healthy right-handed man was found by his roommate lying in the shower, awake and with eyes open, but not speaking or following commands. According to the roommate, he had complained of headaches for at least 1 day prior to presentation, which was unusual for him. The patient's parents remarked that he had seemed normal while speaking the previous day. He was absent from work the day of presentation prior to being found. He had received no recent vaccinations nor had any recent illnesses. He was taken to a local emergency department.

Upon initial assessment in the emergency department, the patient was tachycardic with heart rate of 126 beats per minute, hypertensive at 154/82 mm Hg, and febrile with a temperature of 38.6°C. He was profoundly diaphoretic and noted to have an erythematous, papular rash on his bilateral arms and legs. Mental status examination was significant for lethargy, with language examination revealing him to be globally aphasic (nonverbal and unable to follow simple or complex 1-step commands). Motor examination revealed marked axial and appendicular rigidity with normal reflexes, but grossly preserved antigravity strength. Cranial nerve, sensory, and cerebellar examinations revealed no focal findings.

### Questions for consideration:

1. What is the differential diagnosis for the presentation of acute encephalopathy in the setting of rigidity and fever?
2. What diagnostic tests would you perform?

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## Section 2

The differential at this point was quite broad; given the acuity, fever, and encephalopathy, primary concern was for bacterial or viral meningoencephalitis. Intoxications such as methamphetamine, MDMA, or cocaine overdose were also considered. The rigidity, hyperthermia, and autonomic instability raised suspicion for neuroleptic malignant syndrome (NMS) or serotonin syndrome, though the absence of hyperreflexia or spontaneous clonus pointed more towards NMS. Inflammatory conditions such as autoimmune encephalitis or acute disseminated encephalomyelitis (ADEM) were considered as well. The time course was believed to be atypically rapid for autoimmune encephalitis, which usually develops over days to weeks. A single cerebrovascular lesion would be unlikely to explain global aphasia without causing other focal dominant hemispheric dysfunction, but a multifocal vasculopathy such as primary or drug-induced vasculitis was considered.

Pertinent serum studies revealed a leukocyte count of 28 $\times 10^9$/L, creatinine of 3.0 mg/dL, and creatine kinase of 688 IU/L. Urine toxicology testing was positive for cocaine metabolites. A head CT was performed and showed no abnormalities. Subsequent lumbar puncture revealed mild lymphocytic pleocytosis in the CSF with leukocyte count of 19 $\times 10^9$/L, but normal erythrocyte, protein, and glucose. Gram stain was negative, and comprehensive infectious studies, including herpes simplex virus 1 and 2, were sent.

The patient was started empirically on acyclovir, ceftriaxone, and vancomycin for coverage of typical causes of infectious meningoencephalitis and admitted to the intensive care unit. Serial creatine kinase revealed a peak elevation to 11,000 IU/L; in the setting of persistent rigidity and autonomic instability, he was also started on dantrolene for empiric treatment of possible NMS. Over the course of several days, his fevers and rigidity improved, but he remained encephalopathic and globally aphasic. Final CSF infectious studies were all normal.

### Questions for consideration:

1. How do these data and further clinical course alter the differential diagnosis?
2. What further tests are most appropriate to pursue?

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## Section 3

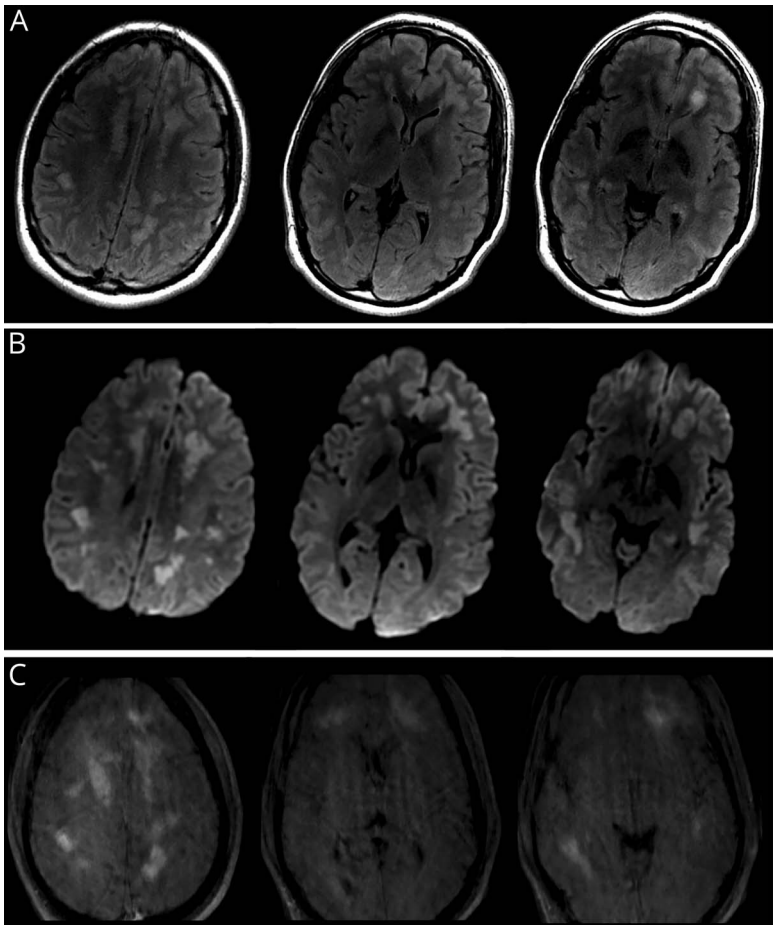
The persistence of profound encephalopathy, resolution of systemic illness, and time course removed from cocaine ingestion led to consideration of further organic CNS pathology. Infectious encephalitis was still considered despite negative studies, though treatment with antimicrobials had not improved encephalopathy and was therefore considered less likely. The CSF pleocytosis supported an inflammatory etiology, such as ADEM, or autoimmune encephalitis. Likewise, a CNS vasculitis, particularly in the setting of cocaine use, was also considered. Given the presence of cocaine in the urine, a coingestion causing a toxic leukoencephalopathy was also considered.

Antinuclear antibody titer was positive, but comprehensive serum autoimmune and vasculitic profiles were otherwise unremarkable. A second lumbar puncture performed 4 days after admission again showed lymphocytic pleocytosis, but repeat infectious studies were again negative. On day 8, a brain MRI with gadolinium revealed T2/fluid-attenuated inversion recovery (FLAIR) hyperintense multifocal ovoid lesions in the subcortical white matter (figure, A) with associated restricted diffusion (figure, B) and moderate enhancement (figure, C). Magnetic resonance angiography of the intracranial and extracranial vasculature was normal.

### Questions for consideration:

1. What is the most likely diagnosis?
2. What treatment would you initiate?

**Figure** Neuroimaging at time of presentation




Axial MRI T2/fluid-attenuated inversion recovery images show multiple irregular and ovoid hyperintensities in the bilateral subcortical white matter (A), with diffusion-weighted imaging confirming diffusion restriction (B) (apparent diffusion coefficient not shown), and enhancement on T1 sequences after gadolinium administration (C).

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## Section 4

The imaging was highly suggestive of an inflammatory leukoencephalopathy. ADEM was considered, but was believed to be less likely given the accompanying systemic features and MRI appearance. ADEM may be bilateral, but usually asymmetric, and often has diffusion restriction in the periphery of lesions, not throughout as in our case. An autoimmune encephalitis, which typically shows a predilection for the mesial temporal lobes and hardly ever has diffusion restriction, was not consistent with the imaging findings. In discussion with our radiologists, considering the known cocaine ingestion, rash upon presentation, and rhabdomyolysis with NMS-like presentation, the diagnosis was most consistent with levamisole-induced toxic leukoencephalopathy due to levamisole-contaminated cocaine ingestion. Cocaine-induced vasculitis was believed to be less likely with normal vascular imaging, and the ovoid and irregular shape of the lesions in nonvascular or watershed territories.

Our patient was treated with 1,000 mg of IV methylprednisolone for 5 days, and discharged to begin rehabilitation shortly thereafter. At follow-up 2 months after the acute admission, he had no discernible deficits; repeat MRI at this time showed persistent T2 hyperintensities with resolved diffusion restriction and enhancement.

## Discussion

Levamisole is an imidazole derivative used as an antihelminthic agent, previously combined with 5-fluorouracil to treat colon cancer in the 1990s, and still occasionally used to treat certain autoimmune disorders in some countries. Levamisole is also still used by veterinarians to deworm animals (e.g., cattle). It is known to augment the immunologic response by activating macrophages, T cells, and increasing levels of interleukin-2.[1] It was pulled from the US market in the early 2000s by the Food and Drug Administration due to cases of agranulocytosis, but more recently has been found to be a common adulterant of cocaine. Cocaine samples were first found to contain levamisole 15 years ago, and by 2009, 69% of samples were contaminated, according to Drug Enforcement Administration estimates.[1]

Levamisole-associated multifocal inflammatory leukoencephalopathy (MIL) has been described in several case series with levamisole use for the aforementioned clinical purposes[2–4] and may present with subacute focal neurologic deficits, encephalopathy, and aphasia. Onset has been noted to manifest from several days to weeks after ingestion. Interestingly, the majority of cases in levamisole-associated MIL have occurred in levamisole-naive individuals[2–4]; our patient reported no prior cocaine exposure. Potential systemic complications include rash, peripheral vasculitis, and agranulocytosis; rash was present in our patient. Laboratory results are notable for variably positive inflammatory markers, especially in the presence of peripheral manifestations, such as antinuclear antibody (similar to our patient) and antineutrophil cytoplasmic antibody (ANCA).[1] Presence of concomitant human neutrophil elastase positivity (ANCA) has been demonstrated to discriminate cocaine-induced midline destructive lesions from primary autoimmune vasculitis when PR3-ANCA was positive,[5] though this has not been studied specifically in cases with CNS manifestations. CSF profile ranges from bland to mild pleocytosis and protein elevation.[3,4] Typical MRI findings include multifocal white matter lesions that may be oval or irregularly shaped, hyperintense on T2, isointense to hypointense on T1, with diffusion restriction and partial to ring-like enhancement.[2–4,6] Radiographically, it can be difficult to distinguish levamisole-associated MIL from ADEM or multiple sclerosis, particularly since it has been known to recur upon re-exposure to levamisole,[2] and therefore clinical context is integral in making this diagnosis.

In 2011, the aforementioned features were noted on MRIs of cocaine users with a similar leukoencephalopathy, and it was suggested that since it was increasingly common in the majority of cocaine samples, levamisole was likely the causative agent rather than cocaine itself.[7] It was not until 2017 when the first published report of MIL in a cocaine user with direct laboratory confirmation of levamisole exposure appeared.[6] In our case, the acute presentation was more likely a direct toxic effect of the cocaine causing an NMS-like presentation,[8] whereas the delayed encephalopathy after NMS resolved was a result of the onset of inflammatory demyelination, and thus too late after ingestion to confirm levamisole exposure; levamisole is detectable for only 39 hours after ingestion,[9] making direct causality difficult to prove. Pathologically, brain biopsies in cases of levamisole-associated MIL revealed demyelination and lymphocytic perivascular cuffing, suggesting an immune-mediated pathogenesis.[4]

In terms of treatment, most patients demonstrate a positive response to immunosuppression, with nearly all patients showing improvement in reported case series.[3,4] Radiographically, improvement in enhancement and restricted diffusion has been reported, though persistent T2/FLAIR hyperintensities are common.[3] In our patient's case, he had excellent response to pulse corticosteroids initiated within a week of symptom onset. Repeat levamisole exposure should be discouraged, as recurrence may occur. Finally, as evidenced by this case, atypical presentations of suspected ADEM should prompt historical and laboratory drug screening for new-onset cocaine use causing levamisole-associated MIL.

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### Disclosure

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## Appendix Authors

| Name | Location | Role | Contribution |
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