Clinical Reasoning:

A 40-year-old man with tremor and seizure

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SECTION 1

A 40-year-old healthy right-handed man presented to the emergency room with loss of consciousness after a nearly 2-month history of progressive involuntary right arm movements and difficulty with fine motor tasks. He first noted a right hand tremor 7 weeks prior to presentation while playing basketball. He then noted clumsiness, with a tendency to drop objects out of his right hand. About 5 weeks after the

initial symptoms he experienced an episode of transient numbness in his right hand, radiating up his arm to his neck. Ten days later, he experienced another episode of numbness in his right hand and arm, extending up to his face and accompanied by facial weakness and impaired speech.

Question for consideration:

1. What is the differential diagnosis of the patient's presentation up to this point?

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(A) CT of the head revealing the hypodensity with sulcal involvement. (B, C) MRI of the brain revealing abnormal fluid-attenuated inversion recovery signal and enhancing nodules. (D) Chest x-ray revealing enlarged hila. (E) Ophthalmologic examination revealing retinal pigment epithelial detachment. (F) Lung pathology slides.

SECTION 2

On the day of presentation, the patient had a simple partial seizure consisting of rapid, shock-like facial jerks and blinking, involving the entire right face but also synchronous with left facial twitching. Following this, he experienced an episode of right arm shaking that radiated to his face, followed by whole body stiffness. He felt his body fall to the ground and he made a moaning type sound. He awoke to find himself on the ground and was brought to the emergency room.

In the emergency room, he noted that he had bitten his tongue. He otherwise felt that he had returned to his baseline except for some right hand numbness. On ex-

amination, he was noted to have a small scalp swelling in the parietal area. He displayed a disabling jerky high amplitude irregular postural and action tremor (video on the *Neurology*[®] Web site at www.neurology.org). There was slight weakness on examination of the right arm. In addition, he had some subjective numbness to light touch in the right arm. Routine laboratory examinations were unremarkable. CT of the head showed an area of hypodensity in the superior posterior left frontal lobe with sulcal involvement (figure, A).

Question for consideration:

1. Which diagnostic studies should be obtained?

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SECTION 3

Once admitted to the hospital, complete blood count, basic metabolic panel, liver function tests, international normalized ratio, partial thromboplastin time, and serum angiotensin-converting enzyme (ACE) were unremarkable. He underwent a lumbar puncture and the results were as follows: zero cells, glucose was 74, protein was 35, ACE was 0.4. Video EEG revealed mild and rare slowing in the left central-parietal region suggestive of possible underlying cerebral dysfunction in this region but there were no epileptiform discharges or seizures. He underwent MRI with and without contrast which demonstrated a large region of abnormal fluid-attenuated inversion recovery (FLAIR) signal in the deep and subcortical white matter of the left frontal and parietal lobes

with minimal local mass effect and the presence of enhancing nodules (figure, B). There were also foci of hyperintense FLAIR signal in the left thalamus, left subinsular region, and right parietal white matter (figure, C). Radiologically, the differential included infectious or inflammatory cause, including acute disseminated encephalomyelitis, tuberculosis, or sarcoidosis; CNS lymphoma and other neoplasms as well as other autoimmune processes were considered less likely.

Questions for consideration:

1. What further testing should be considered to evaluate the brain lesions?
2. How might an ophthalmologic examination help with the diagnosis?

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SECTION 4

We obtained a chest radiograph to look for a systemic cause for the brain lesions. The chest radiograph showed enlarged hila bilaterally (figure, D). Chest CT revealed clusters of nodules in a peribronchovascular distribution mainly in the upper and midlung zones as well as extensive mediastinal lymphadenopathy, most consistent with sarcoidosis. The patient subsequently underwent pulmonary bronchoscopy, which confirmed the diagnosis of sarcoidosis (figure, F).

Of note, an ophthalmologic examination revealed multiple 100–200 μ m retinal pigment epithelial detachments but no evidence of uveitis (figure, E).

The patient was then treated with IV methylprednisolone 1 g daily for 3 days and was discharged on an oral steroid taper. He presented for neurology follow-up 9 days postdischarge. While still present, the tremor was less disabling; the patient was now able to hold onto objects in the right hand.

He had an outpatient computerized tremor analysis, which characterized the movements as myoclonus and tremor. EMG of the right arm revealed short duration (25–50 msec) discrete, irregular discharges likely cortical in origin and consistent with myoclonus. It also demonstrated tremors at rest (3–6 Hz) and with posture (4–9 Hz) thought to be subcortical in origin. Handwritten spiral analysis revealed irregular 3–5 Hz tremors both in the x-y plane and pressure axis, as well as intermittent, abrupt changes in velocity consistent with myoclonus.

Question for consideration:

1. How does neurosarcoidosis present?

DISCUSSION CNS involvement occurs in 5%–10% of sarcoidosis patients.^{1,2} Neurosarcoidosis presents with a multitude of neurologic manifestations (table).^{2,3} The most common presentation of neurosarcoidosis is cranial neuropathy, accounting for 50%–55% of patients, with cranial nerve VII involvement being most common.^{1,3} Central diabetes

insipidus is the next most common presenting neurologic symptom.³ In addition, MRI reveals meningeal involvement in 40% of cases, typically within the basal leptomeninges.¹ Periventricular and white matter lesions account for another 40% of cases, while intra-axial masses account for only 10% of neurosarcoidosis.¹

Our patient's initial presentation with tremor, numbness, facial weakness, dysarthria, and alteration of consciousness suggested a multifocal process. A predominantly left hemispheric localization was suggested because of partial seizures involving the right side of the face and the right arm. MRI showed the presence of white matter lesions in the left superior frontoparietal region, left thalamus, left subinsular region, and right parietal region. These findings were consistent with an active process involving cortical and subcortical regions. Lymphoma, tuberculosis, sarcoidosis, and postinfectious demyelination were among the possible diagnoses.

We thought that CSF studies might aid in the diagnosis. CSF findings vary widely in neurosarcoidosis cases. Increased protein is found in 52% and monocytic pleocytosis in 43%, while oligoclonal bands may be seen in as many as 27% of cases.⁴ None of these findings were present in our patient, but when present, they might also confuse the diagnosis of neurosarcoidosis and multiple sclerosis (MS) because both diseases present similarly. As clinical presentations may be similar, MS should be considered in the differential diagnosis especially in the face of ambiguous CSF findings. However, the chest imaging in our patient made MS a highly unlikely diagnosis in this case, even prior to biopsy.

Our patient had serum and CSF ACE values in the normal range. A recent study found the sensitivity and specificity of serum ACE to be 83.3% and 66.7%, respectively.⁵ The sensitivity and specificity of CSF ACE in patients with suspected neurosarcoidosis are 55% and 94%, respectively.⁶ Thus, clinicians should not rely heavily on ACE values to make this diagnosis, as highlighted by our patient.

We opted to do a chest radiograph to help evaluate the brain imaging findings as 97% of neurosarcoidosis cases have other systemic manifestations, most commonly pulmonary manifestations, occurring in 88%.² This revealed possible hilar lymphadenopathy. Chest CT revealed a potential granulomatous source for tissue diagnosis without a brain biopsy.

Prior to the chest CT being obtained, we consulted ophthalmology to evaluate for possible ocular involvement. If there was ocular involvement we might consider conjunctival biopsy and avoid a more invasive surgery, such as brain or lung biopsy. Conjunctival biopsy has a 14%–40% diagnostic yield in

Table Neurologic manifestations of sarcoidosis	
Cranial neuropathies	Peripheral neuropathy
Encephalopathy	Dural involvement
Meningitis	Psychosis
Seizures	Cavernous sinus thrombosis
Intracranial space-occupying lesion	Ischemic stroke
Neuroendocrine dysfunction	Intracranial hemorrhage
Hydrocephalus	Myelopathy/radiculopathy
Headache	Myopathy
Vasculitis	Tremor

patients with biopsy-proven nonocular sarcoid, with higher yields in patients with follicles or uveitis.⁷ Furthermore, the incidence of neurosarcoidosis increases to 37% in sarcoid patients with ocular involvement.⁸ Uveitis is the classic ophthalmologic finding in sarcoidosis, occurring in 25%–50% of patients with chronic sarcoidosis. Our patient demonstrated no signs of uveitis but instead had retinal pigment epithelial detachment, which has been described in 2 other sarcoidosis patients. One occurred 13 years after diagnosis and steroid exposure, which complicated the evaluation of its etiology, while the other occurred at the time of patient presentation.⁹ While rare, retinal pigment epithelial detachment should be looked for along with uveitis when trying to establish a diagnosis of sarcoidosis.

Response to IV methylprednisolone and other glucocorticoids varies. Alternative immunosuppressive therapies with evidence of some efficacy include methotrexate, cyclophosphamide, cyclosporine, azathioprine, and hydroxychloroquine.^{1,3}

A thorough review of the literature found one prior documented case of neurosarcoidosis presenting with tremor.¹⁰ Our patient experienced myoclonus in addition to tremor, reinforcing and adding to the list of presenting symptoms of neurosarcoidosis. Furthermore, this case demonstrates the varied presentation of sarcoidosis, underscoring the diagnostic challenge of diagnosing neurosarcoidosis when involved organ systems are clinically silent. We believe our patient's case argues for the inclusion of sarcoidosis in the differential for any gradual onset focal neurologic deficit regardless of its character, including tremor and myoclonus.

AUTHOR CONTRIBUTIONS

Dr. Minen: conception and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript and critical revision of the manuscript for important intellectual content, administrative, technical, or material support. A. Rodman: conception and design, acquisition of data, drafting of the manuscript, analysis and interpretation of data, critical revision of the manuscript for important intellectual content. Dr. Foreman: conception and design, acquisition of data, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, administrative, technical and material support. Dr. Motiwala: conception and design, analysis and interpretation of data, crit-

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DISCLOSURE

Dr. Minen, A. Rodman, Dr. Foreman, and Dr. Motiwala report no disclosures. Dr. Pullman serves on scientific boards for Musicians with Dystonia and the Dystonia Medical Research Foundation; serves on the editorial boards of *Neurological Bulletin* and *Tremor and Other Hyperkinetic Movements*; holds a patent re: System and method for clinically assessing motor function; conducts motor physiology studies (40% effort), performs intraoperative mapping for deep brain stimulator implantation (20% effort), administers botulinum toxin (30% effort), and performs EMG studies (10% effort); receives research support from the NIH, Parkinson Disease Foundation, and the Michael J. Fox Foundation; and receives royalties for technology re: Computerized spiral analysis from Columbia University. Dr. Weiss reports no disclosures. Dr. Ford serves on a scientific advisory board for Medtronic, Inc.

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