Clinical Reasoning: A 34-year-old man with headache, diplopia, and hemiparesis

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SECTION 1

A 34-year-old right-handed man awoke with lethargy, headache, diplopia, bilateral facial numbness, mild right hemiparesis, and right arm numbness. A few weeks prior, he had received vaccines for influenza and hepatitis. His history was significant for chronic sinusitis. Family history was negative for neurologic and autoimmune disease.

On examination, the patient was afebrile and normotensive. He exhibited left abducens and partial left oculomotor palsies. MRI of the brain showed an extensive area of fluid-attenuated inversion recovery (FLAIR) hyperintensity involving the brainstem bilaterally and a few smaller lesions in the left parietal lobe (figure 1). There was no enhancement or abnormal diffusion.

Lumbar puncture revealed normal leukocytes ($3 \times 10^6/L$), protein, and glucose. CSF oligoclonal bands were absent. Serum studies revealed normal erythrocyte sedimentation rate (ESR) (18 mm/h) and C-reactive protein. Markers of systemic inflammation were normal.

Diplopia resolved over 10 days without treatment. Other symptoms improved within 3 weeks. On follow-up 4 months later, the patient complained only of mild headaches and mild chest tightness, possibly reflecting sensory banding. Examination was normal apart from minimal difficulty with tandem gait.

Questions for consideration:

1. What is the differential diagnosis?
2. What therapies would you consider?

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Figure 1 MRI brain (January 2009)

Axial fluid-attenuated inversion recovery (FLAIR) MRI demonstrates an extensive area of hyperintensity involving the pons bilaterally (A); this also involved the left medulla and extended into the midbrain bilaterally. Additional FLAIR hyperintensities are noted in the subcortical white matter of the left and, to a lesser degree, right parietal lobes (B).

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SECTION 2

The patient presents with an acute polysymptomatic syndrome referable to the midbrain and pons. Though sudden onset would be consistent with a vascular etiology, the subsequent near-complete improvement over 3 weeks would argue against ischemia. Brainstem glioma or CNS lymphoma may present with similar clinical and imaging features, but not typically in such an acute fashion. Hemorrhage into a pre-existing neoplasm frequently presents acutely, but hemoglobin breakdown products should be visible on MRI or in CSF. Posterior reversible encephalopathy syndrome may produce similar symptoms and imaging findings, but there was no hypertension and no other risk factors. Venous sinus thrombosis is an important clinical consideration, but the imaging is atypical.

Inflammatory etiologies to consider include multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), Behçet disease, Sjögren disease, and neuromyelitis optica spectrum disorder (NMOSD). While multiple sclerosis commonly produces brainstem lesions, they are not usually so confluent. There was no history of oral or genital ulceration to support Behçet disease, which may occur with isolated neurologic manifestations.¹ There was no history of sicca to argue for Sjögren disease. While neurosarcoidosis may produce white matter changes, leptomeningeal disease is more common. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) may produce similar symptoms, but MRI typically reveals punctate enhancement peppering the pons² rather than the more confluent pattern seen in this case. Brainstem encephalitis may cause similar lesions on MRI, but these are typically associated with fever and systemic signs.

The clinical and imaging characteristics are in keeping with ADEM.³ Though unusual in adult patients, this is well-described following immunization or infection.⁴ While diagnostic criteria for ADEM in adults have not been validated, consensus criteria have been published for use in children⁵ (table); these require a polysymptomatic presentation due to presumed inflammatory or demyelinating disease with concurrent encephalopathy. Irritability, lethargy, or other personality changes represent mild encephalopathy.

Acute therapy for ADEM is supportive, though corticosteroids are frequently used. Disease-modifying therapies are not indicated, as patients who recover from the acute episode typically do not experience recurrent symptoms.

Back to the case. The patient recovered fully over several months. Approximately 1 year after his initial presentation, he returned with subacute headache, confusion, aphasia, diplopia, and unsteady gait. On examination, he was afebrile and normotensive. He was drowsy but able to follow simple commands. There was expressive aphasia. Neurologic examination revealed right abducens palsy, right upper motor neuron facial weakness, and bilateral extensor plantar responses.

An MRI scan revealed extensive T2/FLAIR hyperintensities throughout the temporal white matter bilaterally, with lesser involvement of the frontal, parietal, and occipital lobes (figure 2) and midbrain. There was no significant enhancement following gadolinium contrast administration.

Lumbar puncture revealed pleocytosis ($186 \times 10^6/L$, initially neutrophil-predominant and later lymphocyte-predominant) with elevated protein (0.78 g/L) and normal glucose (3.0 mmol/L). CSF cultures

Table Consensus clinical criteria for pediatric acute disseminated encephalomyelitis (ADEM)⁵

A first clinical event with a presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS. The clinical presentation must be polysymptomatic and must include encephalopathy, which is defined as one or more of the following:

Behavioral change, e.g., confusion, excessive irritability.

Alteration in consciousness, e.g., lethargy, coma.

Event should be followed by improvement, clinically, on MRI, or both, but there may be residual deficits.

No history of a clinical episode with features of a prior demyelinating event.

No other etiologies can explain the event.

New or fluctuating symptoms, signs, or MRI findings occurring within 3 months of the inciting ADEM event are considered part of the acute event.

Neuroimaging shows focal or multifocal lesions, predominantly involving white matter, without radiologic evidence of previous destructive white matter changes:

Brain MRI, with fluid-attenuated inversion recovery or T2-weighted images, reveals large (>1 – 2 cm in size) lesions that are multifocal, hyperintense, and located in the supratentorial or infratentorial white matter regions; gray matter, especially basal ganglia and thalamus, is frequently involved.

In rare cases, brain MRI shows a large single lesion (≥ 1 – 2 cm), predominantly affecting white matter.

Spinal cord MRI may show confluent intramedullary lesions with variable enhancement, in addition to abnormal brain MRI findings specified above.

Reproduced with permission from Krupp et al.⁵ *Neurology* 2007;68(16 suppl 2):S7–S12.

Figure 2 MRI brain (December 2009)

Axial fluid-attenuated inversion recovery MRI reveals extensive white matter hyperintensities extending throughout the supratentorial white matter. The anterior temporal lobes are severely involved bilaterally (A), with patchy involvement of bilateral frontal, parietal, and occipital lobes (B). The midbrain is also involved, in a pattern similar to the previous study.

and PCR were negative. Oligoclonal bands were again absent. CSF flow cytometry revealed a nonspecific, polyclonal population of lymphocytes and monocytes. Repeat investigations for systemic autoimmune disease were negative, including ESR, antinuclear antibodies, extractable nuclear antigen screen, rheumatoid factor, and antineutrophil cytoplasmic antibodies screen. Serum angiotensin-converting enzyme was normal and CT chest was negative for lymphadenopathy.

The patient's symptoms gradually improved with a course of high-dose IV methylprednisolone combined with plasma exchange. Oral prednisone was tapered over 5 months and he made a near-full recovery with a normal neurologic examination. Repeat MRI of the brain was also normal.

Questions for consideration:

1. What is the differential diagnosis now?
2. Is therapy indicated at this time?

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SECTION 3

The recurrence of acute, multifocal demyelination causing a polysymptomatic presentation with encephalopathy raises the possibility of multiphasic ADEM. Multiphasic ADEM is conceptualized as a self-limited, transient multiphasic demyelinating disease that does not lead to lifelong, chronic demyelinating disease.⁵ While this is recognized in a subset of pediatric patients with ADEM, many patients who recur subsequently develop a chronic demyelinating disorder.³ Diagnostic criteria for multiphasic ADEM have recently been revised; relapses beyond a second encephalopathic event are now considered suggestive of a chronic demyelinating disorder such as MS or NMOSD.⁶

The principal diagnostic consideration at this time is between multiphasic ADEM and MS. The fulminant nature of the 2 attacks, combined with full resolution, both clinically and radiologically, are more typical of multiphasic ADEM than MS. Significant CSF pleocytosis and absence of oligoclonal bands, present in 85%–95% of patients with MS, also argue against this diagnosis.

Returning to the case. Disease-modifying therapy was not instituted and the patient was followed with frequent clinical and MRI examinations. He remained clinically and radiologically stable for 2 years before he developed several small, asymptomatic demyelinating lesions consistent with possible MS. He continued to develop additional asymptomatic lesions before a third acute presentation with nausea, vertigo, right facial numbness, right facial weakness, dysarthria, right hemiparesis, and right-sided limb ataxia. MRI revealed large demyelinating lesions involving the right middle cerebellar peduncle and left pons (figure 3) along with a small lesion in the left

frontal lobe. Anti-aquaporin-4 channel antibody was not detected in serum.

At this point, a clinical diagnosis of MS was made. The development of asymptomatic demyelinating lesions is characteristic of MS and is not seen in ADEM. A third attack of demyelination would not be consistent with revised criteria for multiphasic ADEM.⁶ The patient was started on disease-modifying therapy for MS and has been free of relapse for over 1 year. He had normal results on neuropsychological testing.

DISCUSSION We describe a case of MS that presented with recurrent episodes of acute, fulminant demyelination associated with encephalopathy and suggestive of multiphasic ADEM. Though the subsequent clinical history has been more consistent with MS, there are multiple unusual features that point to a possible spectrum of inflammatory disease activity.

ADEM is conceptualized as an acute, typically monophasic disorder that frequently follows infection or immunization and presents with multifocal CNS demyelination, encephalopathy, and CSF lymphocytic pleocytosis with elevated protein but typically without oligoclonal bands.⁷ Though histopathologic data from modern cases are limited, the pathology is believed to consist of perivenous sleeves of demyelination with significant associated inflammatory infiltrates and macrophages that form confluent plaques with indistinct margins.⁸

In contrast, MS is typically characterized by the sequential development of symptomatic or asymptomatic periventricular demyelinating lesions. Polysymptomatic presentations are atypical, and encephalopathy distinctly unusual. Spinal fluid may be normal or reveal a mild lymphocytic pleocytosis; oligoclonal bands are typically present. Acute demyelinating lesions exhibit variable perivascular inflammation, lipid-laden macrophages, and reactive astrocytes.^{8,9} The margins of MS plaques are typically more distinct than those of ADEM.

The present case is unusual for the multiple large, concurrent demyelinating lesions. At presentation, there was no evidence for previous asymptomatic demyelination and asymptomatic lesions were not detected until several years after initial presentation. Complete clinical and radiologic recovery following severe attacks is unusual for MS and is more commonly seen in ADEM. On the other hand, while the fulminance of the attacks is unusual for MS, each of the patient's symptoms may be seen individually in otherwise typical MS. This case illustrates the occasionally significant clinical overlap that may exist between MS and ADEM and, together with overlapping histopathology, argues that these disorders may best be conceptualized as falling on a single spectrum.

Figure 3 MRI brain (January 2014)

Axial fluid-attenuated inversion recovery MRI demonstrates a new large hyperintense lesion occupying the right middle cerebellar peduncle (A) with extension into the right superior cerebellar peduncle and right pontine tegmentum. A second lesion also involves the left pons (B) and cerebral peduncle.

The therapeutic implications of this spectrum are not yet determined. While recurrent episodes of severe demyelination frequently leave patients with residual deficits, there are insufficient data from clinical trials to favor the use of any particular prophylactic therapy. Immunosuppressive agents are frequently used in a variety of demyelinating conditions, but further research is needed to determine their relative effectiveness in each of these disorders. The use of MS disease-modifying therapies has not been thoroughly studied in ADEM, owing to the typically monophasic clinical course and rarity of relapse. Data from neuromyelitis optica, in which MS therapies may produce clinical worsening,^{10,11} argue for caution with these agents in this unusual clinical situation.

AUTHOR CONTRIBUTIONS

Matthew R. Lincoln: drafting/revising the manuscript, analysis and interpretation of data. Raphael Schneider: drafting/revising the manuscript, analysis and interpretation of data. Marika J. Hohol: drafting/revising the manuscript, analysis and interpretation of data.

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