It's all in her head: a girl with transient neurologic symptoms.

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History of Presenting Illness

The patient is a 13 year old female with a history of Crohn's disease and mental illness who presented to the ED with progressively worsening intermittent ataxia, dizziness, diplopia, increasing somnolence and dysphagia over three weeks.

ED visit #1 (2 weeks prior)
- Prompted by psychiatric provider for abnormal speech, fatigue, and generalized weakness
- Symptom free, normal exam. Unremarkable basic labs. No imaging.

Seen by PCP (~10 days prior)
- Symptoms progressing, especially gait disturbance and dysphagia.
- Referred to neurology

Pediatric Neurologist (1 week prior)
- Symptom free, normal exam except Romberg.
- Symptoms are worse at school, associated with anxiety.
- Parents voiced concern about confounding mental illness
- MRI ordered and recommendations given to family to work with her psychologist.

ROS:

- General: (+) Fatigue, (+) somnolence , no fevers.
- HEENT: (+) diplopia, (+) throat discomfort and (+) dysphagia to solids and less so liquids.
- Cardiac: No lightheadedness, chest pain or palpitations.
- Respiratory: No difficulty breathing.
- GI: (+) Intermittent vomiting, (+) increased LLQ abdominal pain, no change in ostomy output.
- Skin: (+) painful rash on bilateral lower extremities.
- MSK: no joint swelling or muscle pain.
- Neuro: (+) frequent falls without injury, (+) dizziness, (+) numbness of feet, (+) dysarthria, (+)aphasia, no headache, no head trauma or LOC.

Past Medical and Surgical History

- Crohn's disease complicated by refractory perirectal abscess w/ rectovaginal s/p Seton placement as well as diverting colostomy
  - Failed multiple biologics
  - On chronic suppressive metronidazole.
- Anemia
- Short stature
- Asperger's syndrome
- ADHD/ODD
- Depression
- Bipolar disorder
- Anxiety
- Sleep apnea s/p T&A

Medications

- Lisdexamfetamine 70 mg PO daily
- Risperidone 1.5 mg PO twice a day
- Sertraline 25 mg PO daily
- Mercaptopurine (5 mg/mL) 7.5 mL PO at bedtime
- Metronidazole 500 mg PO three times a day
- Nutritional supplement drink
- Multivitamin PO daily
- Ascorbic Acid 500 mg PO daily
- Folic acid 1 mg PO daily
- Simethicone 125 mg PO as needed for gas

Family and Social History

- Sister and maternal grandfather with bipolar disorder
- Mother with hypothyroidism and hypertension
- Sister with rheumatoid arthritis

- Lives at home with mother and stepfather.
- She is in middle school and excels.
- Denies drug and alcohol use.
- Is not sexually active.

- No recent travel.

Additional Questions?

Physical Exam

- BP 121/74 mmHg | Pulse 113 | Temp(Src) 37.1 °C (98.8 °F) | Resp 23 | Wt 33.6 kg | SpO2 98%
- General: alert, cooperative, conversant. Completely oriented.
- ENT: **3 small posterior pharyngeal ulcerations,** normal dentition, MMM.
- Lymph: no cervical or axillary lymph nodes palpated.
- Lungs: normal respiratory effort, CTA
- Heart: RRR without murmur, symmetric radial pulses, well perfused.
- Abdomen: soft, ND, BS present, no masses, **TTP in LLQ** near healthy appearing ostomy site.
- Skin**: 4-5 discrete 1 cm tender erythematous non-blanching slightly raised lesions scattered on LE bilaterally.**
- Neuro: cranial nerves II-VI intact, muscle tone normal, muscle strength normal, rapid alternating movements normal, finger to nose normal, gait, including heel, toe, and tandem walking normal
- Psych: affect normal, very talkative and interactive, fixates and perseverates on future possible medical tests.

Polling Question Instructions

1. Search for **Clinical Conundrums Presentations Session 1** in the mobile app using the search bar or in the agenda layout.
2. Select the session to open the session page and select “Live Polls”.
3. Answer the question under “Live Polls” by selecting your desired answer(s).
4. Select “Finish” to submit your answer.

What is your initial top differential diagnosis?

A. Crohn's flare with atypical extraintestinal neurologic manifestations.
B. Neurosarcoidosis.
C. Benign Positional Vertigo.
D. Recurrent toxic ingestion.
E. Multiple Sclerosis.
F. Psychosomatic/Conversion disorder.

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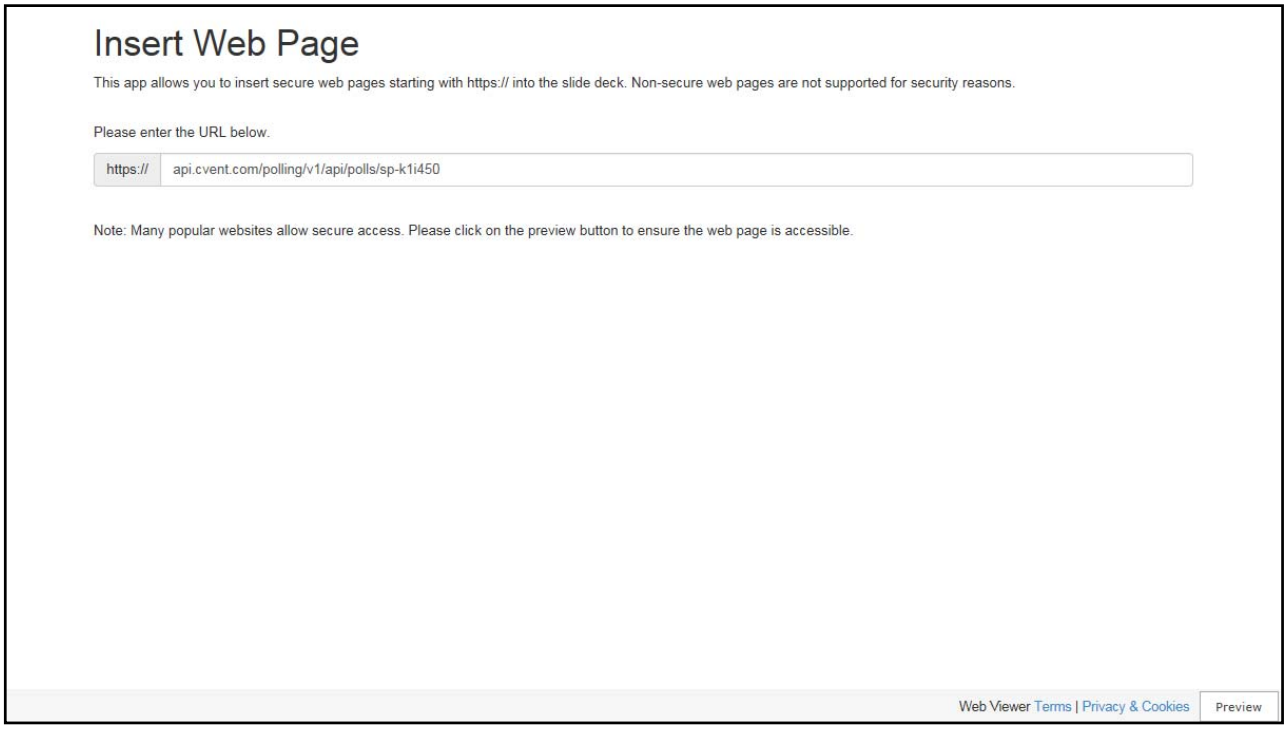


Initial Differential Diagnosis

- Crohn's flare with atypical extraintestinal neurologic manifestations.
- Sarcoidosis with central neurologic involvement.
- Other autoimmune vasculitides with central neurologic involvement.
- Benign Positional Vertigo.
- Repeated TIAs
- Recurrent toxic ingestion.
- Multiple Sclerosis.
- New brain mass.
- ADEM.
- Post-infectious cerebellar ataxia.
- PANDA.
- Psychosomatic/Conversion disorder.

Basic labs and imaging obtained in ED:

135 mEq/L	105 mEq/L	7 mg/dL	115 mg/dL
3.8 mEq/L	24mEq/L	0.57 mg/dL	

Ca: 8.8 mg/dL	TSH: 7.81
Phos: 4.2 mg/dL	FT4: 1.21
Mg: 2.0 mg/dL	ESR: 86 mm/hr
AST/ALT: 17/10 u/L	CRP: 35.1 mg/L
Alb: 3.7 g/dL	B12: 620 pg/mL

12.2 g/dL
11.2 k/µL
472 k/µL
36.1 %

N: 75%
L: 13%
M: 11%
E: 1%

CT head, without contrast:
Impression:
Patchy low attenuation in bilateral basal ganglia with minimal if any local mass effect. No associated hemorrhage. This is a nonspecific finding which can be seen with demyelinating disease (such as ADEM), acute infection, collagen vascular disorder, and intracranial vasculitis.

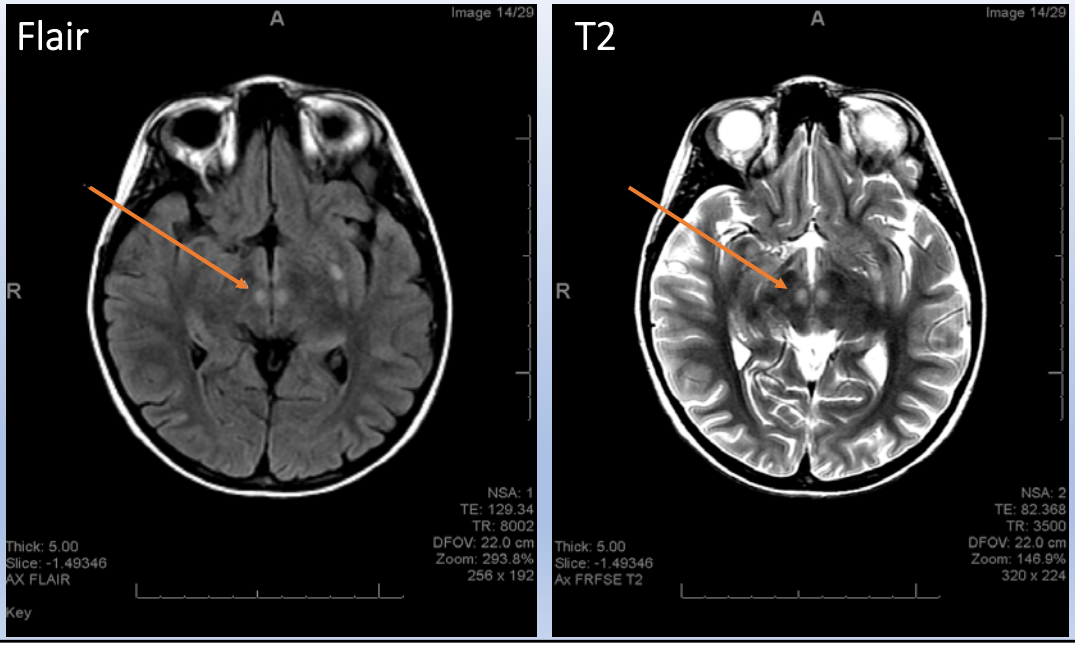
Hospital Course Continued

- Throughout admission, she remained symptom free other than fatigue.
- Given her extraintestinal IBD manifestations (ulcers, erythema nodosum) and the abnormal CT findings, a sedated MRI with contrast of the brain was obtained to evaluate for autoimmune related neurologic disease.
- Pt concurrently underwent LP to evaluate for other potential etiologies such as CNS infection and MS.

Hospital Course Continued

- Initial CSF studies were normal, with MBP and oligoclonal bands sent out to a specialty lab.
- MRI of brain
  - Impression: symmetric bilateral edema throughout the midbrain, mammillary bodies and basal ganglia with the majority of enhancement within the mammillary bodies and basal ganglia.

MRI findings:



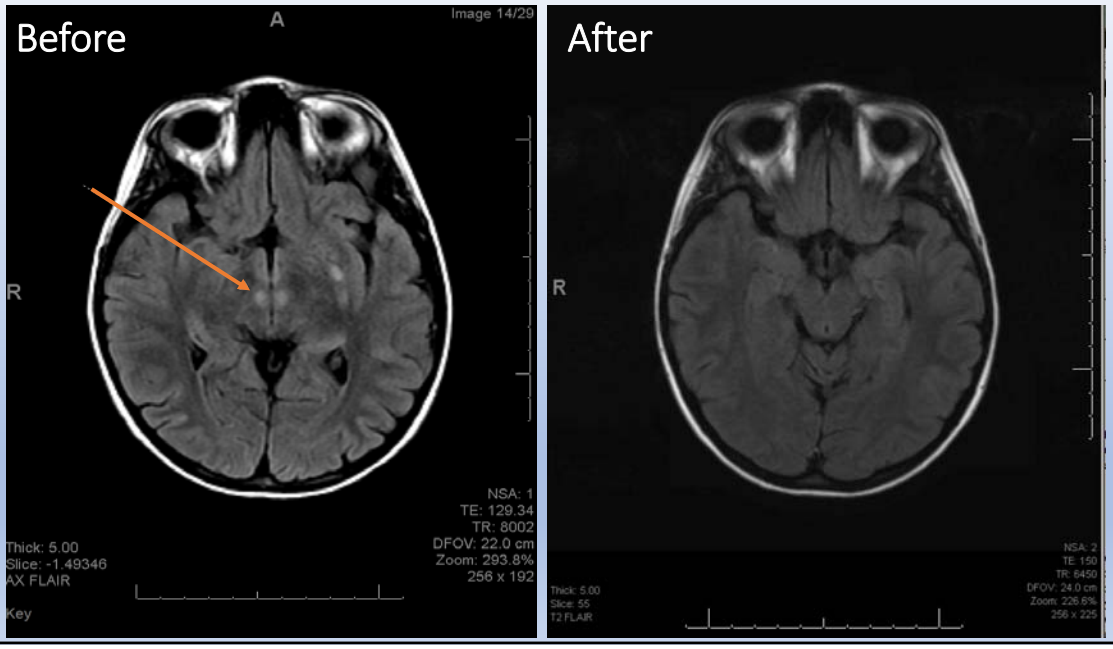
Diagnostic Pause

- Crohn's flare with atypical extraintestinal neurologic manifestations.
- New diagnosis of sarcoid with central neurologic involvement.
- New autoimmune vasculitides with central neurologic involvement.
- Benign Positional Vertigo.
- Repeated TIAs
- Recurrent toxic ingestion.
- Multiple Sclerosis.
- New brain mass.
- ADEM.
- Post-infectious cerebellar ataxia.
- PANDA.
- Psychosomatic/Conversion disorder.

Final Diagnosis

- MRI conclusion:
  - "Findings are most likely due to metronidazole induced encephalopathy. Other possibilities include Wernicke's encephalopathy, metabolic or other toxic encephalopathies"
- Metronidazole discontinued.
- Thiamine empirically replaced.
  - Thiamine level = 13 nmol/L (nl 8-30)
- Seen in follow up by PCP, Neuro and GI.
  - Started on new biologic agent for Crohn's disease.

MRI Comparison at 6 weeks post-metronidazole cessation:



What is Metronidazole-Induced Encephalopathy (MIE)?

- Rare, neurotoxic adverse effect
- Leads to cerebellar and brainstem dysfunction
- Can occur at variable doses and treatment durations

1. Papathanasiou A, et al. *Clin Neuroradiol*. 2013;23(3):217–219
2. Kuriyama A, et al. *Clin Neuropharmacol*. 2011;34(6):241–247
3. Hobbs K, et al. *Neurocrit Care*. 2015;22(3):429–436.
4. Kim E, et al. *Amer J of Neuroradiol.* 2007;28(9):1652–1658.

Why does MIE occur?

Pathophysiology is not well understood

- First described in rats in 1972

Metronidazole is converted to thiamine analog → antagonism

- CNS lesions comparable to Wernicke's encephalopathy.

1. Roy U, et al. *J of Clin and Diag Research*. 2016;10(6):OE01-OE09.
2. Kim E, et al. *Amer J of Neuroradiol.* 2007;28(9):1652–1658.
3. Rogulja P, et al. *Acta Neuropath.* 1973;25:36-45.
4. Alston T, et al. *Archives of Biochem and Biophys*. 1987;257(2):357-362

How does MIE present?

- Dysarthria, Gait disturbance, Dysmetria, Weakness or tingling of extremities, Visual blurring, Seizures, Change in mental status or confusion.

Typical MRI Findings?

- Bilateral, symmetric abnormalities most commonly of the cerebellum and brainstem structures.

1. Kim E, et al. *Amer J of Neuroradiol.* 2007;28(9):1652–1658.
2. Kuriyama A, et al. *Clin Neuropharmacol*. 2011;34(6):241–247.

What is the treatment and prognosis of MIE?

- Immediate drug cessation
- Most cases are entirely reversible
- Rare reports of irreversible neurotoxicity

1. Ahmed A, et al. *Neurol*. 1995;45(3):588–589.
2. Kim DW, et al. *J of the Neurol Sci*. 2004;224(1-2):107–111.
3. Hobbs K, et al. *Neurocrit Care*. 2015;22(3):429–436.
4. Kim E, et al. *Amer J of Neuroradiol.* 2007;28(9):1652–1658.

Wrap Up

- This conundrum represents a common presentation of an uncommon illness.
  - No known pediatric cases of **Metronidazole Induced Encephalpathy** (MIE).
- Fixation of parents and provider's diagnostic reasoning on her mental illness lead to significant **diagnostic overshadowing**.
  - "Misattribution of physical symptoms to mental illness"
- Studies in adult populations show that individuals with mental illness:
  - Are more likely to be misdiagnosed with delayed examination/treatment.
  - Receive significantly less quality of care
  - Are more likely to die prematurely as a result of physical illness, 4-7 fold higher mortality.
  - Pediatric data is lacking

1. Mitchell AJ, et al. *The British J of Psychiatry*. 2009;194(6):491–499
2. Shefer G, et al. *PLOS One.* 2014; 9(11):e111682.

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