CASE STUDY

Delayed diagnosis of myasthenia gravis

CASE SUMMARY

A 71-year-old female patient presented to an urgent care clinic with fatigue, anorexia, and weight loss that had started in the past year. She had a history of frequent UTIs, unexplained night sweats, depression, bipolar disorder, benign pulmonary nodule, hyperlipidemia, GERD, Candida esophagitis, chronic intermittent neck pain with cervical discectomy and fusion, rotator cuff repair and thymoma. The patient had been seen six months prior in her primary care clinic with "intense fatigue and clinical decline" for a couple of months. She had cut back on physical activities and was sleeping 12-14 hours a day.

The clinician entertained a broad differential diagnosis including hypothyroidism, occult malignancy, electrolyte imbalance/ renal failure, lithium toxicity or other medication side effect, or depression. Multiple labs were sent. Most results were normal with two positive findings: Hepatitis C with mildly elevated liver enzymes and mildly elevated ESR CRP.

Over the next month the patient felt somewhat better, although her appetite remained poor. A positive Lyme antibody and confirmatory western blot was done. The infectious disease doctor who was consulted was very concerned that her western blot was highly diagnostic for active Lyme disease, many of the symptoms were consistent with Lyme, and the patient needed to be admitted to the hospital to start a 21-day course of IV antibiotics. However, the infectious disease clinician conducting the inpatient evaluation felt that IV antibiotics for Lyme were not clearly indicated at that time and the patient was discharged on oral doxycycline for three weeks.

Three weeks later the patient was seen as an outpatient by a rheumatologist. She reported feeling much better, although was continuing to lose weight (from 120lbs to 100lbs) with no explanation or suggestion of rheumatology disorders, with continuing night sweats.

Two weeks later she presented to an urgent care center with acute onset of three days severe neck pain/stiffness and jaw pain. A CT neck scan showed no abnormality. She was diagnosed with "muscle strain/spasm" and prescribed cyclobenzaprine which the patient reported was helpful.

One week later the patient presented to urgent care with neck pain and stiffness, but also noted onset of bilateral "shoulder weakness." An MRI head/c-spine was ordered. The MRI showed changes from previous surgery: "anterior cervical discectomy and fusion at C4-5, with decompressed central canal and foramina, mild spondylosis, but no enhancing lesion".

Two weeks later, she presented to her primary care provider, feeling that she was further deteriorating. She complained of pain in her neck, and her arms were weak and she "could not lift anything." She stated her vocal cords were affected. Erythrocyte sedimentation rate and the rest of her labs were normal. The assessment was that there was no clear cause of her symptoms, but they were concerning, particularly in light of her prior cervical surgery. The negative MRI for spinal compression was reassuring but puzzling. The plan was urgent referral to neurosurgery.

Five days later the patient presented to urgent care with symptoms continuing to worsen/progress, including fatigue and continuous weight loss. She reported a lack of appetite and being afraid to eat because of difficulty swallowing and chewing. She had also started to notice double vision. Additionally, she reported feeling like she was having difficulty articulating/forming her words. Considerations included side effect of lithium, but the level returned low. TSH, calcium, potassium values were also normal. Recurrent thymoma was also on the differential (although no evidence of this on CT chest). Also, there was consideration of neuromuscular disorder given upper extremity weakness and difficulty swallowing. Polymyalgia rheumatica or giant cell arteritis were ruled out given ESR/CRP being normal. Polymyositis or dermatomyositis were considerations. Underlying malignancy/ paraneoplastic syndrome also needed to be ruled out.

Three days later the patient was seen by a neurosurgery consultant who concluded this was not a structural spinal issue and was concerned this could be a neuromuscular disease such as myasthenia gravis, given the swallowing difficulty and double vision associated with the symptoms.

The next day she was evaluated in neurology. The exam showed abnormal extraocular movements, with decreased left eye elevation "that was fatigable, with fatigable right ptosis." Jaw opening was mildly weak. Facial weakness was evidenced by incomplete smile, moderately weak cheek puff, and moderately weak eye closure weakness. She had an inability to fully protrude her tongue and moderate tongue weakness, without atrophy or fasciculations. Hearing was grossly intact to conversation. Shoulder shrug and head rotation were normal. An urgent EMG was done which showed severe decrement of amplitude with slow RNS of the facial nerve strongly suggested for myasthenia gravis. Given the degree of dysphagia and neck and arm weakness, the neurologist recommended urgently starting symptomatic and rescue therapy, preferably in a hospital setting.

ISSUES IDENTIFIED

1. Prolonged delay in considering the correct diagnosis

- This resulted in patient suffering more harm than otherwise would have/loss of quality of life and need for rescue therapy
- Rarity of myasthenia gravis resulted in it not being initially considered in the primary care clinic.
- Nonspecific nature of early symptoms
- Many other diseases, also rare, in the differential for such symptoms (i.e., ALS, botulism, etc.)

2. Misleading red herrings and/or coexisting diagnoses

- Atypical presentation and misleading findings
  i. Positive test for Lyme disease – especially confusing since many of the symptoms could overlap and Lyme diagnosis is fraught with confusing symptoms and controversies, especially neurologic symptoms/ complications.
  ii. Neck pain and prior cervical surgery led to initially considering this to be the most likely source of neck pain and arm weakness.
  iii. History of depression/bipolar illness, with initial vague symptoms potentially being due to either mental health issues or medications; when no clear etiology, particularly lab or imaging abnormality was found, clinicians clung to this as most likely "diagnosis of exclusion."
  iv. Premature closure around several of these possibilities.
- How to address the potential for there to be more than one diagnosis/disease present to explain various symptoms? Could the Lyme diagnosis have caused some of the earlier symptoms? This is quite possible.

3. Myasthenia gravis symptoms fluctuate – in general and in this case. The symptoms can worsen over the course of the day (e.g. with activity, may be better in the morning, etc.) or even over days to weeks.

- In the context of a patient with a psychiatric diagnosis, this lent itself to questioning whether these "strangely fluctuating" (thus atypical) symptoms were due to the patient's depression or bipolar illness rather than an unidentified medical illness.

4. The patient had a history of thymoma which should have suggested myasthenia gravis

- Also, with myasthenia, eye muscle weakness and throat muscle weakness when singing or swallowing are common.
- Can be unclear that someone with those issues needs to be sent to neurology rather than ENT or ophthalmology

CHANGE IDEAS

- "Don't miss" diagnosis: myasthenia gravis is a "don't miss" diagnosis. It is both highly treatable and can, if untreated, progress to life-threatening complications. Even though it is rare, this diagnosis should be kept at the top of the list of considerations when patients present nonspecific neurologic symptoms, as well as symptoms more specific for this disease. All doctors need to categorically think about alternatives to Lyme. Always consider whether one may still be missing something if there continue to be symptoms unaccounted for by the diagnosis as there could be multiple issues at play. This is especially key if there are symptoms that are of potentially serious or progressively worsening nature. It would be useful to develop a way to, at a minimum, note symptoms that may have not yet been addressed by diagnoses that have been reached and to list level of uncertainty.
- "Red flags": specific symptoms should serve as "red flags" to trigger the consideration of diagnosis of myasthenia gravis. These include diplopia, "fatigable weakness," and history of thymoma. Could advanced decision support help jog clinicians' memory to suggest myasthenia in case showing these unusual features?
- Care structure: organize care to be more than episodic (eg, sending the patient home with homework questions to answer and follow up with the doctor).
- Situational awareness: might we compile a list of diseases that lead a patient to seem/feel fine one moment, and when examined by the clinician, yet be more serious to not overlook? Examples might include cardiac arrythmias, cataplexy, temporal lobe seizures orperiodic paralysis as illustrative diseases to consider as "fluctuating" syndromes, defying more typical patterns of disease progression or presentation. Armed with situational awareness of such a list of diagnoses, they could be more reliably considered in the differential diagnosis of unusual time courses and negative physical exams.
- Testing – choosing the correct test, which clinicians are not always familiar with, could be prompted by indications-based testing – the clinician writes that they want to test for myasthenia gravis, and the test for presence of antibodies to the acetylcholine receptor and to muscle-specific tyrosine kinase, and/or specific electrophysiological tests are offered as options. The fact that these tests are very specific (i.e., if positive, it is very likely the diagnosis is confirmed), but not always positive (80% sensitivity for serology and electrophysiological investigations) should be highlighted in the results reports for these tests.
- Safety nets: to close the loop on unexplained or unresolved symptoms, we should be proactively following-up with patients, rather than just waiting for them to return if not better. At each step there were opportunities for timely and reliable follow-up (although the final referrals to neurosurgery and neurology were relatively expeditious).
- What can the patient tell us about how she experienced the journey through the system from symptom onset to final diagnosis. Did she feel there were opportunities to do better (wasn't listen to, severity of weakness not taken seriously enough, delays in getting appointments, etc.)

TAXONOMIES

Diagnosis Error Evaluation and Research (DEER) Taxonomy

Where in the diagnostic process an error may have occurred

1. Access/Presentation	a. Failure/delay in presentation b. Failure/denied care access
2. History	a. Failure/delay in eliciting critical piece of history data b. Inaccurate/misinterpreted/overlooked critical piece of history data c. Failure in weighing critical piece of history data d. Failure/delay to follow-up critical piece of history data
3. Physical Exam	a. Failure/delay in eliciting critical physical exam finding b. Inaccurate/misinterpreted/overlooked critical physical exam finding c. Failure in weighing critical physical exam finding d. Failure/delay to follow-up critical physical exam finding
4. Tests (Lab/Radiology)	*Ordering (also called "pre-analytic phase")* a. Failure/delay in ordering needed test(s) b. Failure/delay in performing ordered test(s) c. Error in test sequencing d. Ordering of wrong test(s) e. Tests ordered to be done in the wrong way *Performance (also called "analytic phase")* f. Sample mix-up/mislabeled (e.g., wrong patient/test) g. Specimen delivery problem h. Technical errors/poor processing of specimen/test i. Erroneous lab/radiology reading of test j. Failed/delayed reporting of result to clinician *Clinician Processing (also called "post-analytic phase")* k. Failed/delayed follow-up of (abnormal) test result l. Error in clinician interpretation of test
5. Assessment	*Hypothesis Generation* a. Failure/delay in considering the diagnosis *Suboptimal weighing/prioritizing* b. Too little consideration/weight given to the diagnosis c. Too much weight on competing/coexisting diagnosis *Recognizing urgency/complications* d. Failure/delay to recognize/weigh urgency e. Failure/delay to recognize/weigh complications of a diagnosis
6. Referral/Consultation	a. Failure/delay in ordering referral/consult b. Failure/delay in obtaining/scheduling ordered referral c. Error/suboptimal quality in diagnostic consultation performance d. Failed/delayed communication/follow-up of consultation
7. Follow-up	a. Failure/delay in timely follow-up/rechecking of patient b. Failure to refer patient to close/safe setting/monitoring c. Failure/delay in needed monitoring or lab (BP, INR, repeat CXR) d. Failure/delay in communicating findings among healthcare providers

Reliable Diagnosis Challenges (RDC) Taxonomy

Factors that may have contributed to making diagnosis difficult

1. Challenging Disease Presentation	a. Rare diagnosis b. Atypical presentation c. Nonspecific signs and symptoms d. Unfamiliar/outside specialty e. Masking/mimicking diagnosis f. Red herring misleading finding (history, exam, lab/imaging) g. Rapidly progressive h. Slowly evolving i. Deceptively benign (or intermittent) course
2. Patient Factors	a. Language/communication b. Signal: noise (noisy pts with multiple nonspecific sx) c. Patient failure to share d. Patient failure to follow-up
3. Testing Challenges	a. Test availability, access, cost b. Logistical issues in obtaining, performing tests c. False positive/negative results d. Performance/interpretation challenges e. Equivocal results/reports f. Test follow-up issues
4. Stressors	a. Time constraints b. Discontinuities c. Fragmentation of care d. Memory reliance/challenges e. EMR challenges
5. Broader Challenges/ Failures	a. Recognition of acuity/urgency/severity b. Diagnosis of complication(s) c. Recognizing failure to respond to treatment d. Diagnosis of underlying cause e. Recognizing misdiagnosis

Generic Diagnostic Pitfalls Categories

Clinical patterns/vulnerabilities leading to missed, delayed or wrong diagnosis

1. Diagnosis/Assessment	a. Disease A misdiagnosed/confused with Disease B b. Misled by atypical presentation c. Rare diagnosis: failure to consider or know d. Chronic disease presumed to account for new symptoms (especially in medically complex patients) e. Counter-diagnosis cues overlooked (e.g., red flags, things that don't fit not recognized) f. Drug or environmental factor overlooked as cause of symptoms, or as cause of disease progression g. No specific diagnosis made
2. History/Physical	a. Non-specific/vague symptom(s); hard-to-pinpoint diagnosis b. Intermittent symptoms- overlooked because findings (e.g., exam, lab, EKG) negative when seen c. Failure to appreciate risk factor (or those at risk) for a given disease d. Failure to appreciate limitations of the physical exam
3. Testing	a. Failure to appreciate limitations of a test result(s) b. Failure in follow-up of abnormal/critical result
4. Communication	a. Communication failure with patient, including language barriers b. Failure around communication and ordering of lab tests c. Communication failure between physicians (e.g., PCP-specialist, ED-PCP)
5. Follow-up	a. Failure to monitor, note, or respond to evolving/continuing/persistent symptoms b. Inadequate follow-up visits/referrals, especially in the presence of diagnostic uncertainty
6. Other	a. Urgency of the clinical situation was not appreciated b. Diagnostic findings were masked or misinterpreted due to an intervention or drug (e.g., empiric treatment with oral or topical steroids, PPI, antibiotics, pain medications) c. Problems with inappropriate or over-referral

Cognitive Errors Taxonomy

Selected cognitive biases contributing to diagnostic errors

1. Premature Closure: accepting a diagnosis before it has been fully verified
2. Anchoring: tendency to fixate on specific features of a presentation too early in the diagnostic process and subsequent failure to adjust
3. Confirmation Bias: tendency to look for confirming evidence to support one's hypothesis, rather than disconfirming evidence to refute it
4. Search Satisfying: tendency to call off a search once a piece of data is found, and not considering/searching for additional findings or diagnoses
5. Availability Bias: tendency to give too much weight to diagnosis that come more readily to mind (e.g. recent dramatic case).
6. Base-Rate Neglect: failing to adequately take into account the prevalence of a particular disease
7. Knowledge Deficit (on part of provider)
8. Demographic/Stereotype Bias: Biases from personal or cultural beliefs about women, minorities or other patient groups for whom prejudices may distort diagnostic assessment
9. Other (please specify)

Primary-Care Research in Diagnosis Errors (PRIDE) is an effort to improve diagnostic safety, led by Brigham and Women's Center for Patient Safety Research and Practice in partnership with Gordon and Betty Moore Foundation and the Betsy Lehman Center.

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