

## CLINICAL PRACTICE

*Exercises in Clinical Reasoning***Exhausting the Differential**

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**KEY WORDS:** cerebral aneurysms; motor weakness; dyspnea.

J Gen Intern Med 29(5):808–12

DOI: 10.1007/s11606-013-2730-8

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In this series, a clinician extemporaneously discusses the diagnostic approach (regular text) to sequentially presented clinical information (bold). Additional commentary on the diagnostic reasoning process (italic) is interspersed throughout the discussion.

**A 71-year-old woman was brought by her family to the emergency department with slurred speech for two weeks. Computed tomography (CT) of the brain showed two unruptured aneurysms: a 7-mm basilar tip aneurysm and a 3-mm left middle cerebral artery bifurcation aneurysm (Figs. 1 and 2). She was transferred to a university hospital for urgent treatment of her aneurysms.**

Slurred speech usually results from *dysarthria*, or difficulty with the pronunciation of words; occasionally it is due to *aphasia*, or difficulty with language production. The two entities are readily differentiated by testing naming, repetition, and comprehension, which are preserved in dysarthria and impaired in aphasia. While aphasia is almost always due to a focal lesion in the dominant cerebral hemisphere, dysarthria has a broader localization. Dysarthria may arise from weakness or incoordination in any of the muscles used to produce speech, or from numbness in the oropharynx and tongue. The cause is typically a brainstem or cranial nerve lesion, but dysarthria may also be seen in edentulous, intoxicated, or delirious patients. Associated symptoms implicating the brainstem include vertigo, diplopia, dysphagia, weakness or numbness.

Unruptured intracerebral aneurysms are often incidental findings, but may cause neurological symptoms by compressing a nearby structure, most commonly the oculomotor nerve in the case of a posterior communicating artery aneurysm. This patient's aneurysms are small and not located appropriately to explain her

slurred speech through a compressive mechanism. The larger aneurysm abuts the midbrain, but the cranial nerves that control speech (VII, X, and XII) exit the brainstem from the inferior pons and medulla. Isolated dysarthria without headache would be an unusual presentation for subarachnoid hemorrhage.

*Problem representation is an intermediate cognitive step between data acquisition and generation of diagnostic hypotheses, whereby clinicians develop a concise summary of the key features of the presentation by organizing patient specific information into abstract terms.<sup>1–3</sup> The clinician focuses on the “slurred speech”, which is translated into either dysarthria or aphasia, each of which has a pre-formed illness script (mental representation of disease characteristics) and associated neuroanatomic localization that allows for generation of a differential diagnosis.*

**Intermittent episodes of dysarthria usually lasting less than one hour had occurred for the previous two years. Over the past several months, the dysarthria had become more frequent and prolonged, and for two weeks had been present constantly. Family members described the patient's speech as slurred with a hoarse quality and noted that she was difficult to understand at times. During the past three months, she had developed dysphagia and felt food sticking in her throat, which resulted in a 30-pound weight loss. The dysphagia was most pronounced with solid food, but had recently begun to occur with liquids.**

**She also reported fatigue and shortness of breath for several months, and now felt short of breath when walking more than fifty feet. She denied cough, fever, chills, chest pain, or paroxysmal nocturnal dyspnea, but slept on two large pillows at night to ease her breathing.**

Her dysarthria is intermittent, chronic, and slowly progressive. Stroke and subarachnoid hemorrhage (arising from her aneurysms) would be unlikely to present with this time course. While transient ischemic attacks may cause intermittent neurological deficits, they rarely recur with frequency over such a long time period, and would have been expected to progress to stroke earlier.

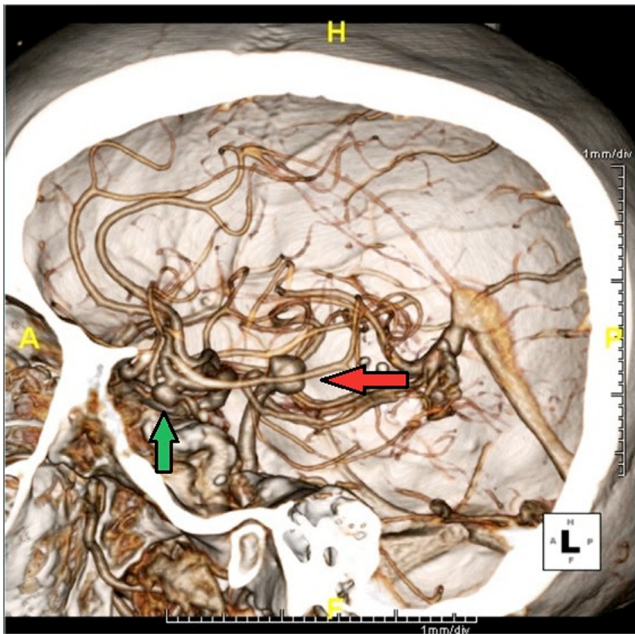
Both dysarthria and dysphagia may be forms of bulbar weakness, and the combination is suggestive of a process involving the brainstem, multiple cranial nerves, neuromuscular junction, or less likely, muscle. A brainstem process may also

Received June 24, 2013

Revised October 25, 2013

Accepted November 21, 2013

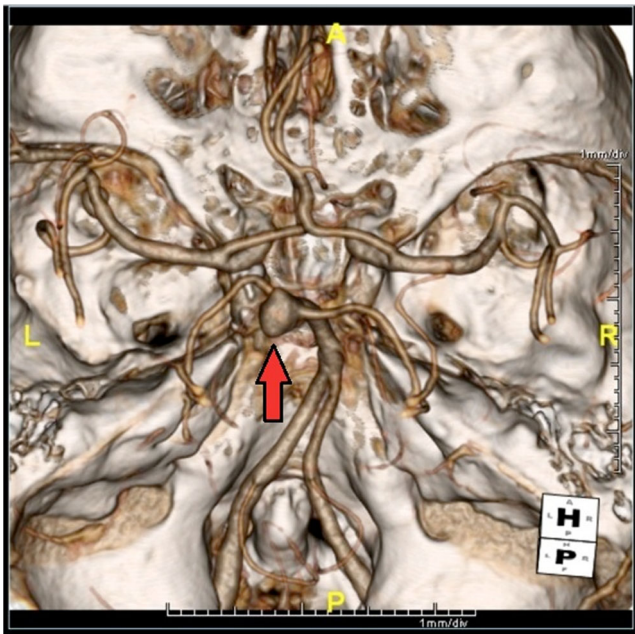
Published online January 7, 2014



**Figure 1.** Computed tomography with angiography of the brain demonstrating a 7-mm basilar tip aneurysm (red arrow) and a 3-mm left middle cerebral artery bifurcation aneurysm (green arrow).

cause upper motor neuron dysfunction in the limbs (spasticity, hyperreflexia, and pyramidal weakness); such signs should be absent in diseases of the neuromuscular junction or muscles, which typically cause proximal limb weakness.

The patient's dyspnea may be explained by weakness of the diaphragm or chest wall muscles. Orthopnea can be observed in neuromuscular disease secondary to diaphragmatic weakness



**Figure 2.** Circle of Willis view demonstrating basilar tip aneurysm (red arrow).

combined with increased resistance from the abdominal contents in the supine position. Alternatively, the patient could have a more common cardiac or pulmonary cause of dyspnea such as heart failure, coronary artery disease, or chronic obstructive pulmonary disease. Because neurological causes of dysphagia usually begin with difficulty swallowing liquids and this patient initially reported difficulty with solid food, a mechanical cause such as a stricture or neoplasm should also be considered.

*All clinicians are at risk of settling on an early diagnosis without fully considering competing hypotheses (premature closure) and preferentially weighting information that supports the initial impression (confirmation bias).<sup>4</sup> While the discussant has given the most emphasis to a unifying neurologic illness, he avoids premature closure by considering more common cardiopulmonary disorders and structural esophageal abnormalities for the patient's individual problems.*

The patient's past medical history included diabetes mellitus, atrial fibrillation, heart failure, hypertension, hypothyroidism, and a left-sided Bell's palsy 30 years earlier. She underwent bilateral blepharoplasties five years previously for acquired bilateral ptosis, though the left eye ptosis had recurred. Her medications were nateglinide, glipizide, insulin, warfarin, metoprolol, losartan, amlodipine and levothyroxine.

She lived with her husband in central California and previously worked as a homemaker. One sister had died from a ruptured intracranial aneurysm in her 40s, and another sister had suffered an intracranial aneurysmal bleed but survived. Her father died in his 70s from intracranial hemorrhage related to an aneurysm. The patient had a 30-pack per year smoking history, but had quit 10 years earlier. She denied any alcohol or illicit drug use.

The history of acquired ptosis could simply represent dehiscence of the tendon connecting the levator palpebrae muscle to the eyelid, but occasionally patients with myasthenia gravis are misdiagnosed with this condition and undergo unnecessary surgery. Her dyspnea could be due to an exacerbation of congestive heart failure, although this would not explain her dysarthria and dysphagia.

The incidence of intracranial aneurysm is approximately 8% in patients with two or more relatives with subarachnoid hemorrhage or aneurysm. Siblings seem to be at greater risk compared to other family members. Her family history is notable, but the aneurysms do not explain her presenting symptoms.

*The availability heuristic distorts the estimated probability of an event and can cause errors in diagnostic reasoning. At the root of this bias is the tendency to misinterpret the most available information or the most memorable information as the most relevant.<sup>5</sup> It is possible the striking family history of cerebral aneurysms influenced the referring physicians to overestimate the possibility (which the discussant has deemed very remote) that aneurysms could account for her neurologic signs and symptoms.*



On arrival to our hospital, the patient became short of breath while walking to the bathroom with an oxygen saturation of 76 % on room air. Her oxygen saturation improved to 93 % with high-flow oxygen administered by a non-rebreather mask. Arterial blood gas (ABG) on 10 liters of oxygen demonstrated a pH of 7.32, a partial pressure of carbon dioxide of 65 millimeters Hg, and a partial pressure of oxygen of 81 millimeters Hg. An ECG showed atrial fibrillation with a rate of 143 beats per minute. A poor-quality chest x-ray revealed low lung volumes. She was given intravenous metoprolol and furosemide. She subsequently became somnolent and difficult to arouse. After brief bag mask ventilation, her mentation improved.

The ABG shows impaired oxygenation and hypoventilation. The elevated alveolar-arterial gradient could be due to pulmonary edema in the setting of heart failure, or possibly atelectasis. Given her dysphagia, aspiration pneumonitis is also possible. There is an element of chronic respiratory acidosis, because a pH of 7.32 with a  $p\text{CO}_2$  of 65 mm Hg suggests a degree of metabolic compensation. The precipitous decline in mentation with oxygen supplementation, and later, her recovery after manual ventilation, is consistent with an underlying chronic respiratory acidosis, either from chronic obstructive pulmonary disease (given her smoking history) or neuromuscular disease. Both can be exacerbated by supplemental oxygen due to a reduction in central respiratory drive.

After stabilization, a complete examination was performed. Her temperature was 37.3 degrees Celsius, heart rate 87 beats per minute with an irregularly irregular rhythm, blood pressure 130/73 mmHg, respiratory rate 26 breaths per minute, and oxygen saturation was 93 % on 6 liters of oxygen by nasal cannula. Her jugular venous pressure was 9 cm H<sub>2</sub>O. There was no thyromegaly or lymphadenopathy. She had normal heart sounds without murmur or gallop. She had crackles in the bilateral lung bases and the abdomen was benign. There was no edema.

Her mental status including language testing was normal. Her pupils were reactive. She had ptosis on the left that did not worsen with sustained upgaze. Primary gaze was disconjugate with the left eye elevated compared to the right, but the extraocular movements were otherwise intact and she did not endorse diplopia. Facial sensation was intact. She had bifacial weakness with difficulty maintaining eye closure against resistance. She had mild to moderate dysarthria. She was able to swallow water without coughing or choking. There were no tongue fasciculations, but she had weakness when pushing her tongue forcefully against the inside of each cheek. She had mild neck flexion and extension weakness. Her extremities had normal tone and strength without fasciculations. Deep tendon reflexes were symmetric. Coordination and sensation exam were normal. Gait was slow but had normal base and stride length.

Bilateral facial weakness and tongue weakness suggests a process localized to muscle, the neuromuscular junction or multiple cranial nerves. A brainstem process large enough to cause bilateral facial and tongue weakness would typically demonstrate more cranial nerve, sensory, or corticospinal tract involvement. Multiple cranial nerves could be affected by acute inflammatory demyelinating polyneuropathy (AIDP) or a disease in the subarachnoid space causing basilar meningitis. The presence of bulbar weakness strongly suggests that her hypoventilation reflects respiratory failure due to neuromuscular disease.

If the ptosis is indeed long standing, it may be a red herring. The hypertropia in the left eye indicates weakness of the left inferior rectus or right superior rectus, but the lack of subjective diplopia suggests this problem is longstanding and may represent childhood strabismus. If the eye findings are part of the current illness, however, unifying diagnoses are limited to myasthenia gravis, oculopharyngeal muscular dystrophy and a few mitochondrial myopathies. Nerve conduction studies with repetitive stimulation and electromyography could clarify the localization and narrow the differential diagnosis.

*The physical exam is used to localize the causative lesion among the brainstem, multiple cranial nerves, or neuromuscular junction as suggested by the history. The combination of ptosis and ophthalmoparesis narrows the differential diagnosis considerably, but the discussant is careful to point out that, much like the aneurysms, these conditions may be longstanding and not necessarily related to the current illness. When considering suspected pre-existing and potentially important findings, the clinician must decide whether they are truly longstanding (and therefore unlikely to be related to the current presentation), or whether they warrant inclusion into the current problem representation.*

Her complete blood count, serum chemistries, and renal function were normal except for a serum bicarbonate level of 32 mmol/L. The B-type natriuretic peptide was 52 pg/mL. Magnetic resonance imaging (MRI) with angiogram confirmed the presence of two aneurysms as previously described and T2 hyperintense lesions in the pons consistent with old small vessel ischemic disease. A lumbar puncture demonstrated one white blood cell, four red blood cells, glucose of 134 mg/dl, and protein of 27 mg/dl. The cerebrospinal fluid (CSF) IgG level and IgG Index were normal.

On the third day of hospitalization, she again became somnolent. A repeat arterial blood gas showed worsening hypercarbia requiring intubation and mechanical ventilation. CT scan of the chest with contrast revealed atelectasis versus pneumonia in the right lower lung but no pulmonary embolism. An echocardiogram demonstrated normal left ventricular function. Her maximal negative inspiratory force was -15 cm of H<sub>2</sub>O (normal < -60 cm H<sub>2</sub>O).

The normal MRI and cerebrospinal fluid exclude an intrinsic brainstem lesion and chronic meningitis, respectively. The weak maximal inspiratory force, together with her neurologic examination, suggests a neuromuscular cause of respiratory failure. The intermittent slowly progressive course with subacute worsening, along with her current clinical findings, suggests myasthenia gravis. Less likely possibilities include a myopathy involving respiratory and facial muscles, or a predominantly bulbar presentation of amyotrophic lateral sclerosis. AIDP or botulism superimposed on another chronic process are monophasic and acute-to-subacute in onset. However, the presence of normal deep tendon reflexes argues against AIDP.

*As the MRI and CSF findings help refine the neuroanatomic localization, the discussant returns to a critical feature of the possible conditions: tempo. Illness scripts contain knowledge of the prototypical and atypical time courses for diseases. The discussant uses the history (episodic slurred speech for two years) and biochemical studies (chronic respiratory acidosis) to characterize the condition as chronic but multiphasic and recently progressive. This profile is more typical of myasthenia gravis than any of the other suspected diagnoses.*

**Nerve conduction study revealed a reduced left facial compound motor action potential and the electromyogram (EMG) demonstrated reduced recruitment in the left facial nerve territory, but was normal in the tongue, left masseter, thoracic paraspinal, arm and leg. Repetitive stimulation could not be completed. The study was interpreted as showing neurogenic change in the left facial nerve territory without evidence of a polyneuropathy or myopathy.**

**She remained intubated for several days while being treated for presumed aspiration pneumonia. She was difficult to wean from the ventilator and her maximal inspiratory force remained below 20 cm H<sub>2</sub>O.**

The nerve conduction study and EMG do not provide a clear explanation for her weakness, but do not show evidence of myopathy or amyotrophic lateral sclerosis (ALS). Myasthenia gravis remains the most likely diagnosis.

*When confirmation of a diagnosis remains elusive, clinicians frequently utilize a strategy of eliminating competing diagnoses. Since the probabilities of all possible diagnoses must add up to 100 %, when the probability of a competing diagnosis is reduced, the remaining diagnoses become more likely.<sup>6</sup> The EMG did not reveal classic findings of myasthenia gravis, but significantly decreased the probability of the competing diagnoses of myopathy and ALS.*

**Acetylcholine receptor antibodies were 36 nmol/L (normal <0.5 nmol/L), confirming the diagnosis of myasthenia gravis. Voltage gated calcium channel antibodies were not detected. Pyridostigmine was administered, and the next morning the patient had modest improvement in strength. She also received a five-day course of intravenous immunoglobulin. CT of the chest and neck with contrast did**

**not demonstrate a thymoma. She improved slowly over several weeks and was eventually discharged home on nocturnal BiPAP and pyridostigmine. Her weakness and bulbar symptoms continued to improve without immunosuppression. Approximately six months later, she developed a pneumonia resulting in a fatal cardiopulmonary arrest.**

## CLINICAL REASONING COMMENTARY

In this case, an elderly woman presented with slurred speech, which led to the discovery of two aneurysms. The symptoms and imaging studies were presumed to be linked and she was referred for definitive treatment of aneurysms, which turned out to be incidental. Consideration of additional historical features and respiratory failure ultimately led to a diagnosis of myasthenia gravis.

Transfers in care are a high-risk time for medical errors, many of which may result from cognitive errors in diagnostic reasoning.<sup>7,8</sup> Multiple providers are involved and are frequently separated in time and space. In addition, information is often lost or temporarily unavailable to the provider assuming care. In this case, although the transfer diagnosis was incorrect, the change in providers afforded an opportunity to reassess the patient and make the correct diagnosis.

Diagnostic momentum can be a source of error during transfers of care. This phenomenon occurs when diagnostic labels are attached to a patient and are accepted without sufficient skepticism. What may be a tentative or preliminary diagnosis by the referring physician may be interpreted as a fully vetted explanation for the patient's clinical presentation. The discussant avoided this pitfall by reassessing the significance of the aneurysms and noting that they were unlikely to explain dysarthria.

The framing effect, which describes how differing subsets of the relevant data (the 'frame') can affect judgments, is one of the factors underlying diagnostic momentum. The transferring physician cannot realistically provide all of the primary data upon which their diagnosis was made, and often frames the presentation by choosing elements both relevant to the diagnosis and persuasive to the receiving doctor. These exigencies may lead to subconscious omissions and/or inclusions of data supporting a given diagnosis among many possibilities.

Both the transferring and receiving clinicians should be mindful of these effects. Transferring providers should convey not only their working diagnosis, but also a narrative of their clinical reasoning. How did they arrive at that diagnosis? What other conditions were considered? How were inconsistencies reconciled? We recommend there be verbal communication between the *original* transferring provider and *ultimate* accepting provider within 24 hours of the patient's arrival. Such a conversation allows for clarifying questions and helps avoid the "voltage drop" that occurs with multiple handoffs and temporary care providers on both ends. Restoration of "warm handoffs" has been suggested as a way to decrease

medical errors.<sup>8–10</sup> While it is impractical to review all the original patient data, the accepting clinician must maintain a healthy level of skepticism of the diagnostic label and follow the axiom, “trust but verify.”

### CLINICAL TEACHING POINTS

1. The risk of intracranial aneurysm rupture is related to the size and location of the aneurysm, with larger aneurysms in the posterior circulation carrying the highest risk.<sup>11</sup>
2. Myasthenia gravis is caused by autoimmune blockade and destruction of nicotinic acetylcholine receptors leading to post-synaptic interruption of neuromuscular transmission. The classic presentation is skeletal muscle weakness (e.g., ptosis, diplopia, dysarthria and/or dysphagia) that increases with activity and improves with rest.
3. Acetylcholine receptor antibodies are found in approximately 85 % of patients with generalized myasthenia. Anti-muscle specific kinase (MuSK) antibodies are found in roughly half of myasthenia gravis patients without acetylcholine receptor antibodies.<sup>12</sup>
4. Standard treatments for myasthenic crisis (e.g. myasthenia gravis complicated by neuromuscular respiratory failure) include plasma exchange or intravenous immune globulin (IVIG).
5. A minority of cases of myasthenia gravis are associated with thymoma or thymic hyperplasia. Thymectomy reduces relapses of the disorder.<sup>13</sup>

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**Acknowledgements:** None.

**Funding Source:** None.

**Conflict of Interest:** Dr. Gaggar has employment and stock ownership with Gilead Sciences.

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