CLINICAL PRACTICE

*Exercises in Clinical Reasoning***A 60-Year-Old Woman with Chorea and Weight Loss**

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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 (*italics*) is integrated throughout the discussion.

CLINICAL INFORMATION

A 60-year-old woman was transferred to our institution for further evaluation of chorea and an unintentional 60-pound weight loss. For the last 6 months she had been experiencing progressive and worsening chorea and clumsiness, which had recently left her wheelchair-bound. She had difficulty speaking and eating because of involuntary movements of her mouth. She complained of intermittent progressive abdominal pain associated with nausea and vomiting. She did not complain of cognitive changes (confirmed with her family), lymphadenopathy, joint problems, skin changes, diarrhea, dyspnea or cough.

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Chorea is an uncommon symptom, especially in older adults. Chorea is described as rapid, semi-purposeful, non-patterned involuntary movements involving distal or proximal muscle groups. Verifying that this is in fact chorea, by personally

witnessing the movements, is important to ensure that it is not a different type of movement disorder.

Movement disorders can be classified as either hyperkinetic or hypokinetic. Chorea is a form of hyperkinetic movement disorder along with dystonia, hemiballismus, and myoclonus. The two most common disorders associated with chorea are Huntington's disease and Sydenham's chorea. A family history of chorea or early cognitive decline would suggest Huntington's disease, which usually shows an autosomal dominant pattern, although it can also present without a family history. Her lack of cognitive changes renders Huntington's disease less likely. Sydenham's chorea is an autoimmune disorder typically occurring in children or adolescents following acute rheumatic fever, and its presentation in this age group would be extremely rare. Wilson's disease is an autosomal recessive illness caused by a defect in cellular copper transport and almost always presents before the age of 30. The disease is characterized by hepatic and neuropsychiatric manifestations, including parkinsonism, dystonia, chorea, ataxia, dysarthria, depression or psychosis. Neuroacanthocytosis is a rare familial disease that may present with chorea and is suggested by the presence of acanthocytes on peripheral smear.

Chorea can also occur in the setting of hyperglycemia; abnormal sodium, magnesium, or calcium levels; hyperthyroidism; vitamin B12 deficiency; any chronic liver disease with hepatocerebral degeneration and following central pontine myelinolysis. Celiac disease and sarcoidosis are also possible etiologies of chorea. Basal ganglia lesions, including those due to stroke, neoplasms, or infectious diseases, such as syphilis, HIV or AIDS-related CNS infections, may also present with chorea. A variety of autoimmune disorders, including systemic lupus erythematosus, Sjogren's syndrome and antiphospholipid antibody syndrome, can cause chorea. Chorea can also occur as a side effect of commonly used medications such as estrogen, methotrexate, prochlorperazine, metoclopramide and other dopamine-blocking agents, and with toxins such as lead, manganese, bismuth, various other metals, amphetamines and cocaine. Paraneoplastic syndromes may present with a variety of neurologic syndromes, including chorea, encephalitis, and cerebellar disease and should be considered given the patient's weight loss. The amount of weight loss is very

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significant and unlikely to be explained solely by decreased oral intake from her movement disorder. Significant weight loss can be associated with neoplasms, depression, or other systemic infections or inflammatory/autoimmune processes.

DIAGNOSTIC REASONING

Clinicians begin the process of generating a diagnosis very quickly when confronting a case, and many times with minimal clinical data. In doing so, they use a variety of heuristics^{1,2} (mental shortcuts used for problem solving) to develop a differential diagnosis. The dual-process theory describes two systems used by clinicians to make diagnostic decisions—the intuitive and the analytical approaches.^{2–5} The intuitive approach is commonly used by experienced or expert clinicians in the diagnostic evaluation of a patient. This relatively quick process is based on pattern recognition after comparing the presentation with known illness scripts. It is implicit, requires little cognitive effort and can use heuristics. For example, an experienced clinician would connect “chorea” with “Huntington’s or Sydenham’s chorea or with systemic illnesses that can present with this symptom.” In contrast, novice clinicians having less clinical experience often use the analytical approach. This approach involves a slow, deliberate, explicit process, developing a step-wise approach to systematically evaluate a patient. For example, the clinician would begin with “movement disorder” and work through a step-wise algorithm. The analytical approach requires considerable cognitive work, and it is the approach medical students and other early learners frequently employ to accurately diagnose patients while they gain clinical experience. Expert clinicians invoke the analytical approach to diagnose a complex patient presentation that does not readily fit into a common illness script, such as this patient represents. Ideally clinicians should use both approaches since they complement each other.⁶ Table 1 compares and contrasts the two approaches, and provides examples from the case discussion.

The clinician recognizes the importance of considerable weight loss and thus utilizes the intuitive reasoning

approach to this symptom. The clinician is not as familiar with the topic of chorea and therefore uses the analytical approach to generate a broad differential diagnosis, of which malignancy is one possibility.^{4,7} Expert physicians are well prepared to transition back and forth between intuitive and analytical approaches, knowing when to “slow down” to spend more time analyzing the available data.⁸ Employing the dual-process theory, the discussant combines both the analytical and intuitive approaches to generate a plausible diagnosis of paraneoplastic syndrome, which could lead to both chorea and weight loss.

Her medical problems included atrial fibrillation, hypertension, hypothyroidism and vitamin B12 deficiency. She was widowed, had a 30 pack-year history of tobacco use and quit 6 months prior. Family history was negative for Huntington’s disease, malignancy and neurodegenerative disorders. She denied alcohol or illegal drug use. Her medications included atorvastatin, digoxin, furosemide, levothyroxine, vitamin B12 and warfarin.

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She carries both the diagnosis of hypothyroidism and vitamin B12 deficiency, which suggests she is predisposed to autoimmune disease. Vitamin B12 deficiency would be an unlikely explanation for her symptoms in the absence of more typical manifestations. If pernicious anemia was the cause of her B12 deficiency, she may be at risk for gastric cancer, which could explain the weight loss. Atrial fibrillation can predispose to basal ganglia infarctions that could result in chorea. Supratherapeutic dosing of levothyroxine could conceivably cause weight loss of this magnitude from thyrotoxicosis. A significant history of tobacco abuse again raises the possibility of malignancy. A paraneoplastic syndrome resulting from a malignancy may be able to tie both the chorea and weight loss together.

On physical examination, she was cachectic, appearing chronically ill, and in no distress. Her temperature was 98.6°F, blood pressure 108/62 mm Hg, heart rate of 74 beats per minute, and the oxygen saturation was 97%

Table 1. Dual Process Framework for Clinical Problem Solving and Diagnostic Reasoning: Intuitive and Analytical Approaches

	Intuitive	Analytical
Speed	Fast	Slow
Cognitive effort	Minimal, unconscious thinking	Deliberate, purposeful thinking
Characteristics	Implicit, employs pattern recognition, first impressions	Explicit, employed when pattern not clear
Requirements	Based on previous knowledge or experiences	Based on knowledge, logic, probabilistic associations and decision making
Biases	More susceptible to context, heuristics and cognitive biases	May be less susceptible to biases
Examples from case	“...common disorders associated with chorea are Huntington’s and Sydenham’s chorea”	“Metabolic disorders, nutritional deficiencies, infections, autoimmune disorders, vascular ischemia, toxins and medication side effects are also possible etiologies of chorea”

Adapted from Croskerry P. Acad Med 2009;84:1022–28

on ambient air. She was alert and oriented. Her heart rhythm was irregularly irregular. Her lungs sounded clear to auscultation bilaterally. Her abdomen was without organomegaly. She had no lower extremity edema, lymphadenopathy or rashes. She displayed oral dyskinesias and severe dysarthria. Her gaze was conjugate and face was symmetric. She displayed choreiform movements in her upper extremities. Motor exam showed 4/5 strength in all four extremities. She had moderate generalized muscle atrophy consistent with cachexia and displayed paratonia in both upper extremities (increased tone that varies irregularly). Her reflexes were 1+ in her upper extremities, absent in her lower extremities, and plantar responses were flexor. Proprioception was decreased at the toes, and vibratory sensation was decreased below the knees of bilateral lower extremities. She demonstrated diffuse allodynia, more prominent in the abdomen. Coordination testing with the finger-to-nose task was impaired due to her upper extremity chorea. Since the patient was wheelchair-bound, gait was not tested. Choreiform movements similar to this patients' can be seen at: (doi:10.1007/s11606-011-1928-x).

Complete metabolic panel, blood count and thyroid function tests were normal. Her international normalized ratio (INR) was 2.3. HIV, RPR, peripheral blood smear and vitamin B12 levels were negative or normal.

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The neurological examination supports the coexistence of chorea and neuropathy. Allodynia suggests that the abdominal pain could be neuropathic. Since the initial laboratory evaluation was non-diagnostic, specific tests for the entities discussed previously should be ordered, such as ceruloplasmin level and copper for Wilson's disease and perhaps genetic analysis for Huntington's disease. Imaging of the central nervous system, lumbar puncture and inquiry of recent age-appropriate cancer screening should be considered. Evaluation for neuropathy should be considered with needle electromyography and nerve conduction studies as well as laboratory markers to investigate common causes, such as vitamin B12 level. Consultation with a neurologist would be appropriate at this time.

DIAGNOSTIC REASONING

The clinician has used both analytical and intuitive clinical reasoning approaches, but is unable to find an illness script that fits well for this patient and recognizes his limitations as an internist confronting a neurological diagnostic dilemma. Since illness scripts are formed according to experience and

contextual knowledge, one physician's collection may be vastly different from another's, especially across specialties. The internist is unable to achieve a unifying diagnosis and recognizes that this patient's presentation may fall into an illness script more familiar to a neurologist; the process of "slowing down" allowed the clinician to consider a broad differential diagnosis and seek expert advice.

Computed tomographic scans of head, chest, abdomen and pelvis with and without contrast were unremarkable. Magnetic resonance imaging showed T1 hyperintensities within the basal ganglia with thalamic sparing, and no areas of ischemia or hemorrhage (Fig. 1). The radiologist commented that this finding could be consistent with heavy metal deposition or atypical encephalitis. The neurology team agreed with the initial workup and recommended additional laboratory studies. Cerebrospinal fluid studies were unremarkable. CEA, CA 19-9 and CA-125 were normal. Manganese, arsenic, iron, ceruloplasmin and copper levels were unremarkable. Anti-phospholipid and anti-tissue transglutaminase antibodies were negative. The electromyographic study showed a mild distal motor neuropathy.

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We have a 60-year-old female with weight loss, chorea, peripheral neuropathy and basal ganglia lesions. The evaluation deems Wilson's disease, heavy metal and medication toxicity, and autoimmune disorders unlikely. Even though multiple tumor markers were negative and multiple imaging

Figure 1. Magnetic resonance imaging (MRI) of the brain with contrast showing T1 hyperintensities in the basal ganglia.

studies were unrevealing, we cannot yet rule out an occult malignancy. It seems she has a systemic illness despite an extensive negative workup thus far. A blood sample should be tested for the presence of paraneoplastic antibodies.

Blood was tested for the presence of paraneoplastic antibodies and returned positive for anti-CRMP-5 IgG at a level of 1:3,840 (negative<1:240).

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Paraneoplastic syndromes manifest as symptoms or findings that are explained by the presence of a malignancy, but that are not produced by a local effect from tumor cells. Examples include hyponatremia from small cell lung cancer or neurological paraneoplastic syndromes due to immune responses against a tumor expressing a certain antigen that cross-reacts with neuron antigens. Paraneoplastic syndromes often precede the diagnosis of cancer. The presence of a paraneoplastic antibody in an individual with a neurological disorder is not necessarily diagnostic of an underlying malignancy. Some antibodies are more likely to be associated with an underlying neoplasm than others. It is important to know how often the antibody is associated with malignancy to determine how thorough the workup for malignancy should be in cases of suspected neurologic paraneoplastic syndromes (Table 2). At a minimum, age-appropriate screening for cancer should be up to date for this patient.

The neurology team, which included an expert in movement disorders, indicated that the presence of the CRMP-5 antibody with the patient's clinical findings supported the diagnosis of "definite" paraneoplastic syndrome; and malignancy has been reported in more than 90% of cases with this antibody.⁹ CRMP-5 antibody has most often been associated with small cell lung carcinoma and thymoma. Her positive result prompted a more detailed oncologic workup. Repeated tomographic scans of the chest, abdomen and pelvis were again unrevealing. A mammogram showed no evidence of malignancy. A colonoscopy had been per-

formed 6 months prior with negative results. Three months after the initial panel was sent, the CRMP-5 antibody titer was repeated and again returned positive.

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Paraneoplastic syndromes are often diagnosed before the primary malignancy is known, as in this case. Since the CRMP-5 antibody appears to be associated with malignancy in over 90% of cases, a very thorough search for underlying neoplasm should be completed. Numerous computed tomography scans, mammography and colonoscopy have been unrevealing. Positron emission tomography (PET) scanning can often diagnose occult malignancies that were not detected with standard imaging. This patient should be considered for a PET scan.

Because of the high index of suspicion of an underlying malignancy despite negative imaging studies, the patient was referred to oncology. A PET scan revealed a 1.5-cm hypermetabolic lymph node posterior to the trachea with a standardized uptake value of 3.4 (normal<2.5). An endoscopic ultrasound-guided fine-needle aspiration was positive for malignant cells that stained for synaptophysin, thyroid transcription factor 1 (TTF-1) and CD56, confirming the diagnosis of small cell cancer of pulmonary origin. The patient underwent four cycles of chemotherapy, lung radiation therapy and prophylactic whole brain radiation therapy. One year following treatment, she had gained weight, was eating well and was no longer wheelchair-bound. Her most recent CRMP-5 antibody titer was negative.

DISCUSSION

In recent years, the cognitive process physicians use to diagnose and manage disease—clinical reasoning—has received renewed interest. The dual-process theory, described in the cognitive psychology literature, has become a

Table 2. Clinical Features Associated with Well-Characterized Neurologic Paraneoplastic Antibodies

Paraneoplastic antibody	Predominant associated neoplasm	Associated paraneoplastic syndrome
Anti-Hu	Small cell lung carcinoma (93%)	Cerebellar degeneration, peripheral neuropathy
Anti-Yo	Ovarian (47%), breast (25%), endometrial (13%)	Cerebellar degeneration, cognitive impairment, peripheral neuropathy
Anti-Ma2 +/- anti-Ma1	Testicular (55%), non-small cell lung carcinoma (21%)	Brainstem encephalitis, atypical parkinsonism
Anti-CRMP-5	Small cell lung carcinoma, (77%), thymoma (8%)	Cerebellar degeneration, chorea, myelopathy, peripheral neuropathy, autonomic dysfunction
Anti-amphiphysin	Small cell lung carcinoma, (59%), breast (35%)	Cerebellar degeneration, stiff person syndrome, cognitive dysfunction, psychiatric symptoms, myelopathy, peripheral neuropathy
Anti-Ri	Breast (43%), small-cell lung carcinoma (24%) and non-small cell lung carcinoma (24%)	Cerebellar degeneration, opsoclonus-myoclonus syndrome, brainstem encephalitis, myelopathy, peripheral neuropathy

Adapted from Gozzard P, Maddison P. *Pract Neurol*. 2010;10:260–70

front-runner model to explain the process of clinical reasoning in medicine.¹⁰ The theory describes two systems used by clinicians to make diagnostic decisions—the intuitive and the analytical approaches. In the intuitive approach, the clinician uses illness scripts to quickly identify common presentations of disorders as described above. The analytical approach describes a slow, deliberate cognitive process that novice learners frequently use. However, experienced and expert clinicians also resort to the analytical approach when confronted with complex patient presentations. Both systems have advantages and disadvantages. While the intuitive approach is efficient, it more frequently results in contextual and cognitive biases. The analytical approach may help clinicians in difficult or atypical cases; however, using this system may lead to “paralysis by analysis.” Ideally, clinicians will use a combination of the intuitive and analytical approaches depending on the complexity of the patient presentation.⁶ As clinicians gain increased experience, their ability to use illness scripts expands. The best clinicians understand that one cannot make every patient fit an illness script. An illness script must be abandoned when key data do not fit the script being considered. At that point, the clinician should slow down and switch to an analytical approach.⁸

The theory and methods of analytical and intuitive reasoning can be introduced through diagnostic exercises to enhance medical education of the cognitive process.¹¹ The fundamental principles illustrated in this case discussion and others^{1,3} can become a framework of medical teaching to help students and clinicians further expand their clinical reasoning skills. We offer a slide set in the online appendix (doi:10.1007/s11606-011-1928-x) for the interested reader to use this case discussion to start or incorporate a clinical problem series discussion at your institution.

CLINICAL TEACHING POINTS

1. Chorea, from the Latin dance or Greek *khoreia*, is a specific type of movement disorder that is characterized by rapid, semi-purposeful, non-patterned involuntary movements.
2. Chorea can be caused by Sydenham's chorea, Huntington's disease, Wilson's disease, electrolyte disturbances,

vitamin deficiencies, neoplasms, autoimmune conditions, toxin ingestions, thyroid abnormalities and paraneoplastic processes.

3. Patients with neurologic paraneoplastic syndromes often will test positive for specific paraneoplastic antibodies, which in turn are associated with certain types of cancer. Thus, the specific antibody found can help focus the evaluation for malignancy.
4. The CRMP-5 antibody can produce chorea and appears to be associated with malignancy in more than 90% of cases.

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