Introduction:

Welcome to CUGH's bi-weekly clinical case-series, "Reasoning without Resources," by Prof. Gerald Paccione of the Albert Einstein College of Medicine. These teaching cases are based on Prof. Paccione's decades of teaching experience on the medical wards of Kisoro District Hospital in Uganda. They are designed for those practicing in low resource settings, Medicine and Family Medicine residents, and senior medical students interested in clinical global health. Each case is presented in two parts. First comes a case vignette (presenting symptoms, history, basic lab and physical exam findings) along with 6-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. Two weeks later CUGH will post detailed instructors notes for the case along with a new case vignette. For a more detailed overview to this case-series and the teaching philosophy behind it, see Introduction to "Reasoning without Resources". Comments or question may be sent to Prof. Paccione at: gpaccion@montefiore.org

Note: If you would like to be notified when a new case is posted (along with instructor notes for the previous one), send your e-mail to Jillian Morgan at jmorgan@CUGH.org.

About the Author:

Dr. Gerald Paccione is a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York. His career has centered on medical education for the past 35 years – as a residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and director of the Global Health Education Alliance at the school. He has served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. Dr. Paccione spends about 3 months a year in Uganda working on the Medicine wards of Kisoro District Hospital where he draws examples for the case studies.

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CASE 36 – Problems Working, Walking, Speaking

A 50 year old plumber, originally from Kisoro but working in Entebbe for the past 20 years, returns to his sister's home in town and comes to the hospital because of difficulty controlling his left arm and speaking clearly for the past 3 weeks.

He had been in good health his whole life with only occasional bouts of malaria until 3 weeks ago when he noticed that he was having problems controlling his left hand while working. Over the week it got worse, and he felt that he couldn't properly direct his hand to pick things up – that his whole left arm would seem to shake getting to its intended object. The following week he started having problems walking, stumbling off balance; to prevent falling he began to walk with his legs apart. He stopped going to work. This past week he began developing problems speaking. His sister was concerned when, over the phone, he was slurring his words, and she sent her son to bring him to Kisoro.

Although his brother-in-law claims he drinks "heavily", all agree that's been 2-3 beers a day for most of his adult life. He's rarely been drunk, and has no history of unanticipated trauma or accidents, withdrawal symptoms or liver disease. He's not been tested for HIV, has been divorced for 10 years, has 2 older children, and is intermittently sexually active usually without condoms. He doesn't have frequent infections, but a year ago had a chest cold with fever and cough for which he was given antibiotics. Since then, he's not had fevers, headaches or pain anywhere, trauma, seizures, weight loss, skin rashes, problems seeing, feeling, or with his bladder or bowels.

Physical Exam: Well developed, middle-aged man in no distress sitting on the bed
BP 120/70 HR: 78 R: 16 T: 98
Skin: no rashes, no zoster scars
Eyes: normal, PERRLA, fundi: benign, without exudates or papilledema
Mouth: no thrush, leukoplakia, purple nodules, petechiae
Neck: supple, no lymphadenopathy, thyromegaly, JVP; Lungs: clear; Heart: normal S1, S2, no murmurs
Abdomen: no hepato-splenomegaly, or masses; Extremities: no edema; pulses normal
Neurologic:

- Mental status: cognition: decreased ability to follow commands, perseverating and intermittently not making sense, unaware of and/or not upset by difficulties
- Cranial Nerves: dysarthric speech, slurring many words;
  left upper temporal quadrant anopsia
  unable to raise shoulder on left
  extra-ocular movements, facial sensation and movement intact
  gag reflex and pharynx and tongue movements normal
- Motor: 4(+)/5 left arm flexion; otherwise normal (repeated many times)
- Sensation: intact to touch, pin, position; (vibration hard to assess)
- Cerebellum: finger-to-nose, marked sway and past-pointing, left>right; dysdiadokinesis abnormal l>r;

- Gait: wide, ataxic; Romberg: (+), can't stand up
- Reflexes: hyper-reflexic upper and lower extremities, mild clonus

1. **What is the "frame" in this case (the key clinical features from the history and exam that the final diagnosis must be consistent with)?**

    - *Constant, progressive, for 3 weeks*
    - *Multiple discrete focal problems: use of left hand, speaking, walking, each worsening*
    - *Cognitive and visual deficits on exam*
    - *No fever, weight loss, or constitutional/systemic symptoms*
    - *No headache*

2. **What is the most important *test* to do promptly, and why?**

    HIV test. The HIV epidemic has changed the context of neurologic evaluation in most of the world, and particularly in sub-Saharan Africa. The HIV virus infects nerves easily and early, and produces a diverse spectrum of pathology involving every part of the nervous system: the brain, spinal cord, spinal roots, and peripheral nerves.
    This patient, apart from a social situation that puts him at risk for disease (a divorced, sexually active, male of 50 years in sub-Saharan Africa) has no clinical symptoms of AIDS and bears no stigmata of HIV on exam. An HIV test would provide the context for evaluating this progressive multifocal disease.

    As expected, the rapid HIV test, done on the day after admission, was positive.

3. **What area of the nervous system is affected in this patient: brain, spinal cord, nerve roots, or peripheral nerves? Explain.**

    The brain: problems with cognition, understanding and vision all indicate the CNS above the cord. The ataxia/imbalance suggests cerebellar involvement, and the hyperreflexia is consistent with upper motor neuron rather than nerve root/peripheral nerve dysfunction.

4. **a) What are the principle causes of neurologic disease in this anatomic location in patients with HIV?**
    b) Which of them present with focal neurologic dysfunction?
    c) How does residence in Africa influence the relative probabilities of disease?

    a) The most common causes (making up > 95%) of HIV-associated brain/CNS disease are the following:
    - *toxoplasmosis*
    - *primary CNS lymphoma*
    - *tuberculous meningitis/tuberculoma*

- *cryptococcal meningitis/cryptococcoma*
- *progressive multifocal leukoencephalopathy (PML)*
- *HIV aseptic meningitis*
- *HIV dementia*
- *Other: stroke/CVA, neurosyphilis (vasculitis/stroke, gumma), cerebral malaria (HIV is a risk for severe, complicated presentations of malaria)*

b) The most common causes of <u>focal</u> CNS/brain disease in HIV are: toxoplasmosis, CNS lymphoma, tuberculoma, cryptococcoma, PML, stoke/CVA - i.e. the above list minus the meningitities, dementia, and cerebral malaria (all non-focal) and neurosyphilis (rare as a cause of focal disease).

c) Africa increases the relative probabilities of tuberculoma (particularly) and cryptococcoma, but toxoplasmosis remains the most common etiology of AIDS-associated focal CNS disease in TB-endemic areas. PML has been reported rarely in Africa, either due to under-diagnosis or HIV-related death prior to development of the disease.

5. What is the *differential diagnosis* in this patient, the diagnostic *pros and cons* for each of the diseases mentioned, and the *most likely etiology* in this patient?

- *Toxoplasmosis (toxo): Toxoplasmosis is the most common cause of focal neurologic disease in AIDS, and due to immunosuppression-induced reactivation of the ubiquitous intracellular parasite acquired from cats and other mammals during youth. Prevalence in the U.S. population is 3-30%, but in France (and probably much of Africa) 75-90%. Incidence of reported CNS toxoplasmosis in AIDS is decreasing, possibly related to TMP-SMX prophylaxis and ART.*
  Toxo presents in late-stage AIDS associated with a CD4 count <100, median 35-50. It starts as a focus of encephalitis that progresses to form parenchymal abscesses with necrosis and surrounding inflammation, and on imaging is usually multifocal at presentation. It presents with an evolution over days-2(+) weeks of progressive headache in >50% , fever in ~50%, and diverse neurologic symptoms including lethargy (10-40%), confusion (15-50%), behavioral changes (~40%), hemiplegia (~50%), ataxia (~30%), cranial nerve palsy (25%) and seizures in 25-30%. It presents with just diffuse encephalopathic symptoms (without focality) in ~10% of cases. If the patient is reliably taking TMP-SMX for OI prophylaxis in AIDS, it decreases the likelihood that the CNS symptoms are due to toxo.
  If examined, the CSF is non-specific with elevated protein and lymphocytes and normal or decreased glucose.
  Often the key to <u>diagnosis</u> is empiric therapy with pyrimethamine-sulfadiazine: ~85% improve clinically by day 7 (and by CT scan, 95% show improvement within 14 days). If unavailable in Africa, high dose TMP-SMX is often effective, but somewhat less frequently.
  In this patient, toxo is unlikely clinically because of the long evolution of symptoms over 3 weeks, and, despite the long duration and multi-focal presentation, the absence of headache, delirium/encephalopathy, fever or constitutional symptoms.

- *Primary CNS lymphoma (PCNSL): CNS lymphoma, due to EB virus, is the second most common cause of focal brain disease in patients with AIDS in developed countries: pre-ART, 4-7% of patients with neurologic complaints had CNS lymphoma diagnosed. Although EBV is ubiquitous in Africa, reliable estimates of the frequency of PCNSL in Africa have been difficult due to the absence of CNS imaging and neurosurgery/brain biopsy (the gold standard).*
  Clinically, PCNSL, though much less common than toxoplasmosis, presents very similarly: in the late stage of HIV disease with CD4 < 50, in patients with other manifestations of AIDS and poor functional status. Most have constitutional symptoms at presentation. Neurologic symptoms and signs include: change in mental status (confusion, memory loss, or lethargy) in 50%; focal motor or sensory signs in ~50%; seizures in 15-40%; cranial nerve palsies 10-20%.
  However, PCNSL usually evolves over a longer period of time than toxo, 3-8 weeks, and is more commonly solitary on imaging (30-50%). Headaches are seen in 5-45%. Thus, compared to toxo, there's a longer evolution of illness, and headaches (and perhaps fever) are less likely, but in general the two diseases are not differentiable clinically without a trial of empiric therapy for toxo.
  In this patient, PCNSL is suggested by the 3 week evolution of focal disease without fever or headache; against a PCNSL diagnosis are the sheer number of separate discrete symptoms/signs that evolved in 3 weeks. This neoplasm, although biologically multi-centric, usually presents with a more limited focal signature.

- *Tuberculoma/Cryptococcoma: TB and cryptococcal meningitis, relatively common in Uganda, can be associated with mass lesions and clinical focality in 5-25% of HIV (-) patients. In HIV (+) patients, tuberculomas are seen in >50%, but fewer than half of these manifest focal findings.*
  These infectious mass lesions would be very unlikely in this patient: both are complications of underlying meningitis which in almost all cases would produce headache, fever, and/or depressed consciousness before (multiple) focal signs would appear.

- *Stroke/CVA: HIV is associated with a significantly higher incidence of stroke. Its pathogenesis is uncertain. Many with AIDS develop anti-phospholipid antibodies, some of which predispose to hypercoagulation. Independent of HIV, silent rheumatic heart disease prevalent in Africa can be a substrate for endocarditis and multiple cerebral emboli. Both are unlikely in this patient: multiple thrombotic strokes in succession would be exceedingly rare, and there were no other symptoms or signs of endocarditis.*

- ***Progressive Multifocal Leukoencephalopathy (PML):*** *This patient manifests the typical presentation of PML, a CNS disorder affecting 1-2% of Western patients with AIDS. It's reported less frequently from Africa possibly due to either under-diagnosis in the absence of imaging, or premature death of AIDS patients from other causes before PML would appear. PML is a demyelinating disease of cerebral white matter caused by the "JC virus", a DNA papova/polyoma virus that infects 90% of the*

population by adulthood, lies dormant in renal and lymphoid tissue, and reactivates in severe immunosuppression: in AIDS, in patients with CD4 counts < 100 usually, but also with CD4 >200 in 10-25% of cases.
Clinically, PML presents over 2-6 weeks with multiple discrete focal deficits, each one gradually worsening from onset, involving gait and coordination (70%), cognition (60%), speech (40%), limb paresis (40%), vision (hemianopia) (30%), sensation (20%), and seizures (15%). (%'s are rounded from nationwide Danish cohort study, JID 2009:199:77-83). Notably absent are symptoms/signs of increased intracranial pressure, headaches, fever, or other constitutional symptoms (unless unrelated to the PML). This patient had most of the typical manifestations noted above, and was without headache or other symptoms of space-occupying infectious or neoplastic processes.

6. What diagnostic "tests" (beyond history and physical exam) are indicated?

Besides the HIV test, two other tests available in rural Africa would be indicated:
1) a CD4 count, which although expected to be low with most of the diagnoses discussed above, would be important in confirming the range of diagnostic possibilities provided (and which, if >100, would support PML over toxo or lymphoma) and in providing a baseline from which to measure the success of ART treatment;
2) evaluation of empiric therapy for toxoplasmosis as a diagnostic test.

Examining the CSF for cells, protein and glucose would be nonspecific given our differential diagnosis and contraindicated in the presence of focal findings that could be from mass lesion(s). If a CT were available and showed no signs of increased intracranial pressure, either CSF culture or PCR for JC virus (PML) or EBV (lymphoma) might be helpful to avoid the need for brain biopsy.

7. What treatment should be offered, and what is the prognosis for this patient?

As noted above, empiric therapy for toxoplasmosis, a remote but rapidly fatal possibility that's treatable, should be provided, and the patient followed closely. If toxo were the diagnosis, improvement should be seen within 1-2 weeks.

Treatment for the most likely diagnosis, PML, has been disappointing even in well-resourced countries. The demyelinated lesions do not re-myelinate, and with few notable exceptions, lost abilities are not regained. In general, the most one can expect is arrest of further progression of the process by re-constituting the immune system with ART.
Prior to ART, the median survival with PML in developed countries averaged ~2 months; post-ART it approaches 2 years. There are reports of worsening of PML due to ART-induced IRIS, but ART therapy should continue in that case (along with steroids) for any hope of longer-term survival at the pre-ART level of function.

Suggested Readings:

Skiest, D.J. Focal Neurological Diesease in Patients with Acquired Immunodeficiency Syndrome CID 2002:34 (1 January) : 103-115

Manji, H., Miller, R. The Neurology of HIV Infection *J. Neurol. Neurosurg. Psychiatry* 2004;75;29-35

Engsig, F.N. et.al Incidence, Clinical Presentation, and Outcome of Progressive Multifocal Leukoencephalopathy in HIV-Infected Patients during the Highly Active Antiretroviral Therapy Era: A Nationwide Cohort Study JID 2009:199 (1 January): 77-83

Koralnik, I.J. Progressive Multifocal Leukoencephalopathy Revisited: Has the Disease Outgrown Its Name? Ann Neurol 2006;60:162–173

Trachtenberg, J.D., et.al The medical management of central nervous system infections in Uganda and the potential impact of an algorithm-based approach to improve outcomes International Journal of Infectious Diseases (2007) 11, 524—530