Introduction:

Welcome to the 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 4-10 discussion questions that direct clinical reasoning and/or highlight diagnostic issues. A month 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

About the Author:

I'm a Professor of Clinical Medicine at the Albert Einstein College of Medicine in the Bronx, New York, where my career has centered on medical education for the past 40 years – as a past residency Program Director in Primary Care and Social Internal Medicine at Montefiore Hospital, and global health advisor and program leader at the school. I've served on the Boards of Directors of Doctors for Global Health, Doctors of the World USA, and the Global Health Education Consortium. I spend about 3-4 months a year in Uganda working on the Medicine wards of Kisoro District Hospital which, like most hospitals in the world that serve most of the world's population, has (almost) no resources. "At the bedside", I teach Internal Medicine residents and medical students how to assimilate the elements of history, physical exam and epidemiologic probability into a diagnostic impression that, even without definitive testing, can lead to appropriate therapeutic strategies in the field.

Gerald Paccione MD
Professor of Clinical Medicine
Albert Einstein College of Medicine
110 East 210 St., Bronx, NY 10467
Tel: 718-920-6738
Email: gpaccion@montefiore.org
Case 60: Headache in a Healthy Man

A 29 year old male presents to Kisoro District Hospital complaining of headache for 8-9 days. For the past 10 years he has worked in both Kisoro and Kampala as a migrant farmer, and is married with two healthy children. He had been fine, without a history of headaches prior to this. The headache began gradually about 8-9 days ago, initially at night and has gotten worse ever since. For the first few days he was able to fall asleep, but would wake up about 5-7 hours later with a more severe headache. For the past 2 nights he has been unable to sleep at all because of the pain.

He has had no weakness or double vision, dizziness, problems walking, speaking or swallowing; he has had diffuse pain “in his muscles” on the right, and upon direct questioning says that bright light hurts his eyes. Two days after headache onset he started feeling nauseated, and has vomited 1-2 times a day. He has had no seizures, fever, weight loss or cough. He had been sexually active outside of his marriage while in Kampala, but not for at least 5 years and has never been HIV tested. He has had no STDs, penile ulceration, or urethral discharge.

Physical Exam: Muscular young man sitting up in bed looking sleepy, yawning; holding his head; T 37; BP 135/85; R 15; HR 60
Skin: no nodules, papules, or pustules
Eyes: normal conjunctiva, no pallor or icterus; +/- photophobia to light;
Fund: no hemorrhages; blurred right disk margin;
Neck: supple in all directions; no lymphadenopathy
Mouth: no thrush; skin normal
Lungs clear;
Heart: PMI normal 5th ICS, MCL; S1 S2 normal, no murmurs, rubs, gallups;
Abdomen: normal without masses or hepato-splenomegaly
Musculo-skeletal: no muscle tenderness; joints normal
Neurologic: CN: EOM intact; pupils equal, dilated in dim light, right pupil responds sluggishly but equally to light, accommodation, and convergence;
CN7: left lower face, partial palsy (when provided a mirror, patient confirmed that the asymmetric grin was new)
Motor: left triceps 5-/5, right 5/5; biceps 5/5 bilaterally
left hamstring 5-/5, right 5/5; quadriceps 5/5 bilaterally;
other muscle groups in forearms, hands, calves, feet 5/5
Sensory, Cerebellar, Gait: all normal

N.B. Patient himself was quite surprised by his left-sided weakness.
1. What is the “frame” in this case (i.e. the key clinical features the final diagnosis must be consistent with)?

- more than 1 week of headache, severe
- insidious onset, progressive, first time
- wakes him from sleep
- subtle focal findings on neurologic exam
- no symptoms of asymmetric motor weakness by history, focal abnormalities only observed on exam (to the surprise of the patient); normal mental status, no seizures
- nausea and vomiting
- young male, Kampala, extra-marital sex in the past

2. What general cerebral process is suggested by the clinical features of the frame? Explain.

The frame suggests mass lesion(s) in the brain expanding fairly rapidly over the past 2 weeks.

The onset and worsening of symptoms at night is classic for headache due to increased intracranial pressure. When supine, the rate of venous drainage from the CNS decreases and, as respiratory drive during sleep also decreases and CO2 rises, cerebral arterioles dilate. The end result is higher intracranial pressure (ICP) further stretching the pain-sensitive meninges and inducing or exacerbating headache.

The nausea/vomiting is a sign of increased intracranial pressure, as is the (probably) blurred disk margin on the right – papilledema.

The focal neurologic exam – differences in motor strength and pupillary responsiveness between right and left, and central deficit of CN 7 (lower facial partial palsy), indicate that there is one or more space-occupying lesions in the right cerebral hemisphere causing the increased ICP. The mass lesion could be infectious (abscess), tumor or hematoma.

The insidious onset over a week and absence of trauma by history strongly auger against a bleed/hematoma. The progression to severe headache over (only) a week augers equally strongly against a brain tumor and for an infectious process.

The neurologic focality by exam only and the absence of mental status change or seizures suggest that the patient is not yet in extremis and there is still “room” for a sequential as opposed to a shotgun approach to empiric therapy.

A young male migrant worker with a distant history of extramarital sex is a strong risk factor for HIV infection in Africa.
3. The initial neurologic exam by the resident did not pick up any focal neurologic signs, but the attending’s exam later did. After the attending elicited the signs, they were confirmed by both resident and student multiple times. What factors might explain the differences between the resident’s and attending’s initial exams?

While it is easy to ascribe the differences to “experience”, and indeed at the most basic level experience is a correct answer, it is not helpful. Specifically, what about “experience” was responsible for the difference and what skill might therefore be adopted by trainees?

First, the approach to the exam was different. Based on the history of a first-time progressive headache worse when supine and now severe, the attending had a very strong suspicion (i.e. high pretest probability) that the patient had increased intracranial pressure, and without imaging available, diagnostic probabilities would hinge on finding evidence of focality. He knew that since the patient did not complain of any particular neurologic impairment (apart from pain “in his muscles” on the right side), any signs that would be found would be subtle.

So the attending approached the exam as if he was sure to find something and pulled and pushed against the patient’s resistance during the motor exam with vigor. He was able to overcome the (muscular) patient on the left side only with considerable force applied – and then do so consistently – but could not overcome him at all on the right. The patient himself was surprised. With the same heightened attention to detail, a subtly asymmetric grin was noted and confirmed by the patient looking in a mirror, the pupillary reflex on the right was seen to be more sluggish, and on fundoscopic exam the right disc not as sharp as the left.

To the more casual examiner, the resident in this case, these signs would be easily missed although they were easily elicited later by the same resident examiner. The attending’s exam was informed by the patient’s history and his attention focused on “finding something”. The resident was performing a more routine exam in a patient with “headache without neurologic complaints”, which in the States, far away from the specific context of this patient in Africa, is a very low-yield exercise.

The attending’s exam was also informed by his prior knowledge that the exam carried enormous weight in the diagnostic equation in this setting, and he had confidence in his observations. The resident, while “knowing” there were no CT/MRI’s available in Kisoro, had rarely if ever put much weight on his neurologic exam – nowadays usually performed on ward admissions after imaging provides an “answer” and robs the exam of nuance or sense of discovery. The resident’s confidence that the exam will provide something new and important was/is vastly diminished, and consequently subtle findings are more easily overlooked as “normal”.

4. What test is key in “orienting” the differential diagnosis?

The HIV test is key. The differential diagnosis changes entirely for CNS mass lesions in HIV positive vs. HIV negative patients. CNS presentations in African young adults are usually HIV-associated.

5. What is the differential diagnosis in this patient?

The differential diagnosis hinges on the result of the HIV test.
If HIV (-) the following diagnoses should be considered:

TB meningitis with tuberculoma
Brain abscess from pyogenic organisms
Neuro-cysticercosis (the larvae of tenia solium, or pig tapeworm) with recent death and degeneration of encysted cysticerci now causing inflammation around the encysted parasites
Brain tumor, glioblastoma multiforme, with bleed into the tumor mass to explain the progressive development of symptoms over only a week
Other: rapid evolution makes uncomplicated brain tumors unlikely, and gradual onset makes intracerebral bleed/hematomas unlikely

If HIV (+) the following diagnoses should be considered, all of which can present with focal findings:

Toxoplasma encephalitis (TE)
Primary CNS Lymphoma (PCNSL)
Tubercular meningitis with tuberculoma (TBM)
Cryptococcal meningitis, with cryptococcoma (CM)
Progressive Multifocal leukoencephalopathy (PML)
Other including:
Brain abscess, other (Staph, Salmonella, Nocardia, Microsporidia, Rhodococcus)
Neurosyphilis, gumma mass lesion

Test: The HIV test was POSITIVE.

6. What are the “pros” and “cons” for each of the potential diagnoses named? What is the most likely diagnosis clinically, and why?

Toxoplasma Encephalitis (TE) is the most likely diagnosis in this patient.

Toxoplasma are unicellular protozoa that are ubiquitous worldwide. Acquisition occurs via ingestion of oocysts from soil contaminated by cat feces or ingestion of cysts embedded in undercooked meats (sheep, pigs, cattle). Prevalence depends on poverty level (i.e. environmental hygiene) and cultural practices: toxoplasmosis (toxo) infects around 20% of the population in the U.S. but 90% in France where undercooked meat is the main risk factor, and most regions of sub-Saharan Africa where contaminated soil is the source of infection.

Usually asymptomatic, toxoplasma cysts disseminate throughout the body and live indefinitely as intracellular parasites kept in check by the immune system. In immune competent hosts toxo can infect the fetus or rarely cause chorioretinitis or a mono-like syndrome in young adults. The quiescent cysts reactivate in severely immunosuppressed HIV patients (CD4 < 200, usually < 100) and, prior to routine prophylaxis of known HIV-infected patients with TMP-SMX, TE was responsible for > 70% of focal CNS infections. Prior to HAART, studies estimated that ~5-50% of latently infected persons would develop CNS TE.

Cerebral toxoplasmosis (TE) accounts for ~90% of the disease manifestations, with about 2-10% involving lung (presenting like PCP), eye or diffuse dissemination including the heart (myocarditis). TE begins as foci of encephalitis which progress to parenchymal abscesses with
surrounding inflammation. About 70% of TE reveals multiple lesions on MRI/CT, and 30% are single. TE has a predilection for the parietal or frontal lobes, the thalamus and basal ganglia, and the cortico-medullary junction.

Clinically, the typical patient with TE has a progressive course over 1-3 weeks of symptoms and signs limited to the CNS. Depending on the reported series of patients, headache, fever, behavioral change-confusion-lethargy, hemiparesis, ataxia, cranial nerve palsies, and seizures are all seen in 20-50% of patients. For the clinician in rural Africa diagnosing without imaging or serologic resources, the “negative” in these numbers is as important as the positive: i.e., 50% don’t have headache; 50% don’t have fever, 50% don’t have symptoms/signs of encephalopathy….In such cases the progressive evolution of neurologic symptoms over weeks in an HIV (+) patient should suggest the diagnosis. More importantly, any patient presenting with the sub-acute evolution of neurologic symptoms over weeks should have an HIV test, and if positive, TE should be considered.

Whether or not the patient is taking TMP-SMX prophylaxis (recommended in ALL patients in Africa with HIV) is definitely germane to the probability that TE is causing the patient’s illness. However prophylaxis is not an absolute predictor of disease: in a pre-HAART decision analysis from Italy, the probability of TE for those receiving prophylaxis with TMP-SMX in sero-positive patients (the majority in rural Africa) and CNS mass lesions was still high at 0.59 - versus 0.87 for those not receiving prophylaxis; but in those receiving TMP-SMX, the probability of CNS lymphoma became a major competing diagnosis at 36%.

This patient was most likely to have TE for a number of reasons: the time course fits; it is prevalent and his work as a farmer in Africa brought him into contact with domestic animals, oocysts and possibly undercooked meat; with a new diagnosis of HIV he was not on TMP-SMX prophylaxis; and the constellation of symptoms – focal motor weakness, cranial nerve findings, and pain on his right side - was consistent with cerebral/basal ganglia/thalamic involvement, all common sites for TE.

Primary CNS Lymphoma:
In the developed world, toxoplasmosis, primary CNS lymphoma (PCNSL) and progressive multifocal leukoencephalopathy (PML) are the 3 most common causes of focal CNS presentations. (In the developing world, tuberculomas and less commonly cryptococcomas are important additional causes of focal CNS presentations.) Since PML (see below) does not cause severe headache or signs of increased intracerebral pressure, PCNSL is the principle alternative diagnosis in this patient.

Like most lymphomas associated with HIV, PCNSL is most commonly a diffuse large B cell lymphoma (immunoblastic variant). Prior to HAART, the CD4 counts in patients with PCNSL were reported to be less than 50 cells/µL, a more severe average degree of immunosuppression than with TE. Thus PCNSL is rarely the initial presentation of AIDS. (In the HAART era, the incidence of PCNSL has decreased markedly, and the average CD4 count on presentation of this now-rare disease has risen to the 100-200 cells/µL range, probably affecting the most susceptible hosts disproportionately.)
PCNSL presents with solitary and multiple mass lesions with equal frequency and has a predilection for the corpus callosum or periventricular areas of the CNS; posterior fossa/thalamic lesions are more likely to be due to infection.

Clinically, the natural history of PCNSL is somewhat longer than TE: PCNSL usually evolving over 1-2 months and TE over 1-3 weeks. Patients present with symptoms similar to toxoplasmosis: focal symptoms of motor weakness and/or aphasia; non-focal symptoms of confusion, lethargy and mental status change; and seizures. Notably, constitutional symptoms of fever, night sweats and/or weight loss are seen in over 80% of patients with PCNSL.

However, other than the time course, degree of immune suppression and symptoms/signs of posterior fossa localization – all of which are only modest predictors of the underlying pathology, TE and PCNSL overlap clinically and cannot be reliably differentiated prior to empiric therapy, special imaging techniques such as perfusion MRI, PET or Thallium SPECT, or brain biopsy. Of these, only empiric therapy is an option in rural Africa.

**TB Meningitis, Tuberculoma**

TB meningitis (TM) is a key consideration in this patient with HIV, and commonly presents with headache (50-80%), vomiting (30-60%), photophobia (5-10%), and hemiparesis (10-20%) – all of which this patient had. And also frequently with symptoms and signs absent in our patient: cranial nerve palsies (30-50%), most commonly CN VI; neck stiffness (40-80%); change in mental status (10-60%), and fever (60-95%) (Lancet Neurol 2005; 4: 160–70). TM causes focal symptoms and signs via a thick basilar exudate that entraps cranial nerves and induces vasculitis that cause infarcts in traversing arteries. Hydrocephalus is a common complication. TM usually evolves over 2-4 weeks prior to presentation, although presentations after 2-3 days of symptoms, mimicking pyogenic meningitis, have been reported - as have very insidious courses over 6 months. HIV disease has not altered the natural history, clinical presentation or the response to therapy of TM. Evidence of active or inactive pulmonary TB is present about 50% of the time.

Tuberculomas are intracranial masses from coalescing granulomas formed in response to hematogenous dissemination of TB during earlier primary infection or later during reactivation and/or miliary TB in adults, particularly HIV-infected adults. As intra-parenchymal masses, when tuberculomas reactivate and become symptomatic, signs of meningeal inflammation are rarely present. However, asymptomatic tuberculomas accompany symptomatic meningitis frequently and are found incidentally by imaging in ~30-60% of HIV-related vs. 10-15% of non-HIV-related TB meningitis. (N.B. Tuberculomas may first become symptomatic during treatment of TB meningitis – called “TB-IRIS” – or in HIV patients after the start of HAART as an HIV-IRIS reaction to quiescent TB.) Thus, in untreated patients, symptomatic disease from CNS TB is usually caused either by meningitis (commonly) or tuberculoma (rarely), but rarely from both simultaneously.

In this patient with HIV, TM or tuberculoma are both possible. However, tuberculoma is much less common than TE, and the 8 day duration of illness, especially with focal signs of partial hemiparesis, is short for TB meningitis. Furthermore, the absence of either meningismus or of impairment of CN V, VI, or VII further diminishes the probability of TM.

**Cryptococcal meningitis (CM):**
It is estimated that there are nearly 1 million cases of CM globally per year, ¾ of them in sub-Saharan Africa, nearly all in AIDS patients with a CD4 count of <100 cells/mm³. CM is the leading cause of meningitis in most areas of East Africa. Similar to TB meningitis, CM classically presents after weeks of fever and headache, but photophobia, vomiting and stiff neck are seen in only 20-30% of cases. Also mimicking TB, cough with pulmonary infiltrates can be seen in 20% of patients (the lungs are the portal of entry for Cryptococcus) and disseminated blood-borne disease is also seen: Cryptococcemia without meningitis can be a cause of FUO in patients with severe immunosuppression, and skin disease in the form of mulluscum-like papules, nodules and pustules can be clues to disseminated cryptococcemia. Altered mentation is seen in about 25% of patients with CM on presentation.

Focality is rare. “Cryptococcoma”, a fungal abscess in the parenchyma can occur causing focal symptoms and signs, but focality is observed in only ~5% of patients presenting with CM.

Our patient had symptoms for only a week, and on exam had focality, no neck stiffness and no skin lesions. CM cannot be clinically ruled out, but is not most likely.

**Progressive multifocal leukoencephalopathy (PML)**

PML is a demyelinating disease caused by the ubiquitous intracellular JC virus that reactivates with severe immunosuppression. Most cases occur with CD4 counts <100, although 10-20% occur with CD4 >200. Affected patients develop multiple discrete defects over 2-6 weeks prior to presentation, each one gradually worsening: gait and coordination (70%), cognition (60%), speech (40%), limb paresis (40%), vision (hemianopia) (30%), sensation (20%), and seizures (15%) (figures are rounded from a nationwide Danish cohort study, JID 2009;199:77-83). Notably absent in this non-inflammatory, non-edematous process are symptoms/signs of increased intracranial pressure, headaches, fever, or other constitutional symptoms. Since in our patient headache was dominant and accompanied by other manifestations of raised intracranial pressure, PML can be ruled out on clinical grounds.

**Neurosyphilis:**

Neurosyphilitic gummas can present as para-meningeal mass lesions, exuberant granulomatous reactions to meningeal foci of spirochete infection. (N.B. Most gummas involve the skeleton, spine or mucosa.) Previously a manifestation of late syphilis taking years to develop, in HIV patients gummas can evolve over months. Although the sluggish right pupil conjured consideration of the Argyll-Robertson pupil of neurosyphilis, unlike Argyll-Robertson’s classic observation, the pupils were not small, and reacted equally to light, accommodation and convergence. Furthermore, gummas are rare, there were no other symptoms/signs of syphilis such as chancre or rash, and the progression of symptoms was too rapid to be consistent with gummatous neurosyphilis.

**Other, Brain abscess, (Staph, Salmonella, Nocardia, Microsporidia, Rhodococcus)**

Other pathogens can involve the brain and cause abscesses, some more common in HIV patients.

Nocardia and Rhodococcus equi cause pulmonary nodules/abscesses and a subacute presentation that mimics TB, and brain abscess are their most common extrapulmonary manifestation.

Microsporidia, obligate intracellular parasites are transmitted by contaminated water. In HIV patients they cause diarrhea, but with CD4 counts <50 infection can disseminate from the intestine to the brain, often accompanied by sinusitis or keratoconjunctivitis. Seizures are common. Spores can be found in peripheral blood and the CSF can demonstrate neutrophilic pleocytosis.
All these infections are RARE, and should only be considered if the patient presents with other manifestations of the infection in question, is in extremis and first-day empiric therapy “can’t miss”, and/or the patient failed to respond to treatment for the far more common disorders discussed above.

7. What tests, available in an African district hospital, would you order in this case?

Beyond a CD4 count, unlikely to be available within days (if at all) in most district hospitals, few tests would be indicated.

A CD4 count would help estimate probabilities of the various OIs discussed and thereby help with choice of empiric therapy, e.g. PCNSL or CM would be unlikely with a CD4 above 100, and with a CD4 above 200-300, CNS TB would be most likely. (However, it should be stressed that infections that can occur at higher CD4 thresholds (like TB or TE) are still most likely to reactivate in patients with lower CD4 counts - they just have more competitors at lower CD4 counts.)

A VDRL or RPR, or FTA-ABS or similar treponemal test for syphilis would be helpful if positive, but in the serum the false negative rate would be high.

A chest x-ray in the absence of symptoms or signs of pulmonary disease would be unlikely to be helpful.

An LP in the presence of signs of intracranial hypertension and focality would be contraindicated. (N.B. In the context of this differential, the CSF analysis would also be unlikely to differentiate between most of the diagnostic possibilities, although India Ink could reveal Cryptococcus in 50-70% of CM, and multiple LPs (x3) done in expert labs can demonstrate AFB in over 70% and low glucose in ~80% of CNS TB.) Otherwise, lymphocytic pleocytosis with raised opening pressure would be expected.

Unfortunately, in KDH at the time, no CD4 count was available. It would have to be sent out to another city in one week, with results expected in two weeks. The VDRL was negative. Chest x-ray not done.

8. How would you treat this patient? Explain/defend your treatment strategy.

The therapeutic decision in this patient and cases like his, is whether to treat only for the most likely diagnosis or all the “dangerous” life-threatening possibilities concurrently.

Since evidence of focal mass lesion(s) was limited to the physical exam only and the patient’s mental status was intact, the team reasoned that “there was time” for targeted empiric therapy with vigilant monitoring a few times a day.

• Since toxoplasmosis was highly probable – much more so than the other diagnoses for reasons discussed above, and since all the treatments have long-term implications, he was treated for the most likely first: with TMP-SMX in high doses, and monitored closely. (N.B. TMP-SMX also covers nocardia and rhodococcus equi (also treated by rifampin).)

• If he had progressed over the next 24-48 hrs (by either symptoms or PE), TB drugs would have been added next, along with steroids. Steroids would certainly muddy the water by non-specifically decreasing inflammation and possibly improving his clinical picture no matter what the etiology. It would buy time, but mandate continued close follow-up and a
wider course of treatment if he deteriorated again in a few days as the underlying infection advanced.

- Cryptococcal therapy is costly, toxic and chronic and therefore shouldn’t be added empirically as part of an initial strategy against multiple (more likely) diseases. Fluconazole alone is fraught with a high failure rate in symptomatic CM, an often-lethal infection despite therapy. Although anti-fungal treatment would have been tried next, a lumbar puncture and India ink prep would have been undertaken before committing the patient to long-term cryptococcal treatment. (There would be little loss of diagnostic accuracy after a few days of treatment and presumably his raised ICP would decrease with steroids.) N.B. Ideally, serum or urine cryptococcal antigen testing, highly specific and sensitive (i.e. >90%) for CM, would have been checked but was not not available.

- If the patient had any suggestion of possible microsporidial infection such as diarrhea, albendazole would also be tried; and depending on the evolving circumstances, treatment for pyogenic bacterial brain abscess might be considered if transfer to Kampala was refused or impossible.

To the team’s immense gratification, the patient responded to TMP – SMX within 2 days and was without headache and focality within 4 days. As he was being advised and mentored about his new diagnosis of HIV and TM, he eloped from the hospital during the 4th night post-admission, taking no medications with him. Three days later he returned, again symptomatic with increasing headache and weakness. In the meantime, he had also become a “believer”. He finished his course of treatment, continued prophylaxis with TMP-SMX, was started on HAART for a CD4 count of 68, and brought his wife for HIV testing... which was negative.

SUGGESTED READING:
Skiest DJ Focal Neurological Disease in Patients with Acquired Immunodeficiency Syndrome Clinical Infectious Diseases 2002; 34:103–15
Holmes, CB et.al Review of Human Immunodeficiency Virus Type 1–Related Opportunistic Infections in Sub-Saharan Africa Clinical Infectious Diseases 2003; 36:652–62
Engsig FN, 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 The Journal of Infectious Diseases 2009; 199:77
Heller, HM Toxoplasmosis in HIV-infected patients UpToDate 2013