



## **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 instructor 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](mailto: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 Katherine Unger at [kunger@CUGH.org](mailto:kunger@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 47 – Three Strange Stories

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- a) 25 year old male, a migrant farm-worker outside of Kampala, experienced the gradual onset over hours of a piercing headache and fever, with diffuse abdominal and joint pains for 2 days. On the third day he could hardly get out of bed, and was taken to a hospital where he was given an IV for “malaria”. He improved and eloped after 2 days. He felt well for 3 days and then began to get sick again with fever and headache. He called his family in Kisoro, who went to Kampala to pick him up where they found him confused, and brought him on the overnight bus to Kisoro. Back home, he slept the morning, but in the afternoon was again making no sense. He didn’t seem “hot”. The following morning, he was fully awake with eyes wide open, but totally mute. All day he stared around but said nothing, and was generally uncooperative. They brought him to the hospital. He had never acted like this and did not drink or use drugs. On physical exam, he was alert, mute, and seemed rigid, all muscle groups resisting passive movement. His temperature was 99.5 axillary; his neck was rigid in all directions; lungs clear; heart S1, S2 normal; abdomen, spleen descended 4 cm on inspiration, soft and non-tender; no hepatomegaly or masses. Neurologic: non-focal grossly; PERRLA; non-icteric, non-cooperative with commands, staring blankly, blinking every 3-5 seconds, mute.
- b) 20 year old male went to Masaka to work the fields about six months ago, his first time away from home. About three weeks ago, he became febrile and was admitted to the hospital with “malaria”. On the 3<sup>rd</sup> day, he slipped into a coma and “meningitis” was diagnosed. Sulfadoxine–pyrimethamine was continued for a day and then penicillin and chloramphenicol were started. He regained consciousness but was confused and began complaining of abdominal pain. He then became aggressive, acting “strange” and hearing voices telling him that his brother who lived in Kenya was getting married. He refused treatment. On about the 12<sup>th</sup> hospital day, he was put on a public bus bound for Kisoro by his friends/caretakers. On arrival in Kisoro he wandered about aimlessly for two days until he was recognized, his family notified, and he was taken home. At home he remained quiet and withdrawn, without interacting with family and not eating for days. His family then brought him to the hospital. According to his family there was no prior patient or family history of bizarre behavior, alcohol or substance use, or complaints of feeling hot, headache, belly pain or cough. On exam, the patient appeared catatonic and motionless, lying on the floor. He suddenly jumped away terrified and screamed when touched; then became calmer but fearful looking and vigilant. His vital signs were normal, with an axillary temperature of 98. He was uncooperative with the exam, but lungs were clear, eyes non-icteric, and neurologic non-focal. His neck

resisted movement in all directions. He was sedated, and an LP attempted unsuccessfully. Thorazine was started. He remained withdrawn and intermittently aggressive, unpredictably. The morning of the 3<sup>rd</sup> hospital day he seized briefly, and post-ictally his temperature was 102.

- c) 21 year old patient was well, working as a migrant laborer in Kampala until 4 days ago when he began talking nonsensically to his roommates. He was able to respond to questions and comments, but often didn't make sense and, when his confusion increased, his friends took him to Church where the congregation prayed for him. He seemed to improve and quiet down, but within a few hours after the Church ceremony, he began moving around inappropriately and acting confused again. He was brought by a friend on the overnight bus to Kisoro where his family could attend him, and they came straight to the hospital on arrival. He had no past medical problems, did not drink alcohol or take drugs, and had never acted strangely before.

On exam, he was surrounded by 3 concerned friends and additional family. He appeared bizarre with a hyper-intense, wide-eyed stare, yelling non-sensical comments and resisting aggressively. His temperature was 98 axillary; he couldn't be approached for a physical exam, but grossly wasn't breathing with distress, was not in pain, and had no neurologic motor paresis. Observing his behavior, he repeated a sequence of "clucking" sounds, spitting, and grunting which could be interrupted by his reactive resistance to an examiner.

**1. What is the common "frame" of these cases (the key clinical features from the histories and exams that they have in common, and that the final diagnosis(es) must be consistent with)?**

- *Young adults native to Kisoro but living away, now brought home with bizarre behavior*
- *First time episodes, previously well*
- *Subacute: 2-12 days of illness*
- *Afebrile (on presentation)*
- *Alert-hypervigilant,*
- *Erratic, unpredictable, changing behaviors*

**2. What factors suggest *schizophrenia* in these patients?**

**Define *encephalopathy*.**

**What factors suggest *encephalopathy* or "organic psychosis" in these patients?**

*Schizophrenia is possible because:*

- *it is common the world over, found in 1-2% of most populations and usually more frequent in the poorer sectors of society;*

- the usual age of onset (adolescence/young adult) fits these patients;
- the overt manifestations are often precipitated by stress. These young men were away from home for the first time;
- patient b's behavior had been bizarre for 1-2 weeks, more than the usual duration of psychoses due to organic illness

*Encephalopathy is a disorder of higher cortical function that typically involves a range of cognitive abilities, including attention, orientation, memory, perception, and language. Alterations in mood, psychomotor activity, and sleep-wake cycle may also be present. (Imitators of Epilepsy, Ch 14 Benetar and Drislane; eds. Kaplan and Fisher, Demos 2005).*

*“Organic” psychosis or encephalopathy is suggested because:*

- it was the first time they manifested a change in mental status; acute schizophrenia is usually associated with a prior history of similar episodes or unusual behavior over months to years
- two of the three had had a recent history of “malaria” or “fever”
- they had received therapies inadequate to treat (almost any) infection associated with mental status changes

### **3. Name at least 5 general causes (categories) of encephalopathy commonly seen in Africa?**

- CNS infection
- Non-CNS infection (sepsis, pneumonia)
- Drug toxicity/side effects
- Substance abuse/withdrawal (e.g. alcohol, etc)
- Non-convulsive status epilepticus (NSCE)

*Less common:*

- Metabolic/organ failure: hypoglycemia, hyperglycemia/DKA, hepatic, renal, pulmonary (hypoxemia), thyrotoxicosis/myxedema, electrolytes (hyper-hyponatremia, hypercalcemia)
- Post-trauma: concussion, subdural

### **4. What are some common errors in causal reasoning made by family and friends when grappling with loved ones in these situations? What are common mistakes made by medical providers that can prove catastrophic?**

- Misdiagnosis of encephalopathy as the work of demons or the devil by family and friends, and as primary psychosis by medically-trained providers.
- Both lead to costly delays in diagnosis, which can be fatal in infection.

*In a medical setting, overreliance on the presence of fever to indicate infection is a common mistake.*

**5. The patients in the vignettes each had TWO causes of encephalopathy, operating at different pathophysiologic levels, that are sometimes difficult to disentangle as explanations for changes in mental status.**

**Can you identify the 2 (identical) causes that each were suffering from?**

**Why are they sometimes difficult to differentiate as the underlying cause of the clinical problem?**

*CNS infection and NCSE (non-convulsive status epilepticus, in these cases “complex partial status epilepticus”).*

*They are often difficult to differentiate because the symptoms of NCSE overlap greatly with encephalopathy, and the NCSE itself is due to the same CNS infection that could itself cause encephalopathy without NCSE.*

**6. What are the similarities and differences observable on exam between most encephalopathies and the condition illustrated by the patients in the vignettes?**

*Non-convulsive status epilepticus (NCSE) involves prolonged seizures (without convulsions) characterized by confusion, speech or language impairment, automatisms, and amnesia. All of these, except for automatisms are seen in all causes of encephalopathy.*

*As with other causes of encephalopathy, the effects of NCSE range from coma (e.g. NCSE is responsible for 8-25% of cases of coma in ICUs), to subtle behavioral changes lasting minutes to weeks, spanning hypo to hyper-alert states.*

*The NCSE that causes behavioral change can be sub-classified as a) **SPSE** (simple partial SE) e.g. when involving the temporal lobes it can manifest as psychosis, or when involving the language centers, as aphasia; b) **CPSE** (complex partial), or c) **absence SE**. The changes range from clearly stereotyped automatisms to more complex “reactive” patterns of semi-purposeful behavior.*

*Some clinical clues that help differentiate encephalopathy from seizure are:*

- *Time course of fluctuations: Although both encephalopathy/delirium and NCSE show fluctuation in mental status, patients with CPSE (whether continuous or intermittent by EEG) can fluctuate rapidly from being vaguely “out of it” but semi-functional to totally unresponsive with staring and speech arrest - over a matter of seconds to minutes. The changes are more gradual with encephalopathy.*
- *Aphasia: although hesitation, reduction in spontaneous speech (even mutism) and word finding difficulty are seen with encephalopathy, aphasia is not. Although rare, all forms of aphasia have been described in NCSE.*

- *Subtle motor signs:* NCSE can manifest subtle motor signs like facial, hand or limb myoclonus, eyelid twitching, or forced head or eye deviation - in about 30-50% of cases. These movements are usually more rhythmic and regular than the asynchronous myoclonic twitches or asterixis of encephalopathy.
- *Automatisms:* Stereotyped, “automatic” behavior patterns are seen in ~50% of NCSE (usually CPSE or absence SE) and are quite specific for seizure over encephalopathy.
- *Response to anticonvulsant medication:* even if transient, a response to IV diazepam, lorazepam or valproate strongly suggests NCSE. Encephalopathy usually worsens. The problem is that many cases of NCSE don’t respond, and sometimes only respond after hours. Furthermore, the effects of benzodiazepines may compound a coexisting encephalopathy making it difficult to arouse the patient after the SE has been broken, leading to other (similar) diagnostic questions.

**7. What is the evidence that the patients in the 3 vignettes above had 2 causes of encephalopathy (“organic psychosis”)?**

**What is the probable *primary etiology* of both in all 3 cases?**

*The underlying cause of the acute psychotic behavior in all 3 cases was cerebral malaria.*

*The patient in case “a”, who had eloped from a hospital in Kampala after partial improvement on quinine days earlier, indeed had a positive paracheck, and later that night spiked a temperature to 102. He was talkative and normal (though without recollection of the preceding days) the following morning after receiving IV Quinine. Patient “b”, who presented over a weekend when the microscope was locked up and before paracheck became available in Kisoro, had a dramatic response to IV quinine and was completely normal within a day. Patient “c” was paracheck positive, spiked a fever to 101, and recovered with treatment for malaria (albeit after more surprises, see below).*

*All 3 presented with cerebral malaria (CM) as young adults. Although CM is seen in adults in hyper-endemic areas, usually it is a fatal disease of the under-5’s. Once past childhood, most have immunity. However migrants from highland “hypo-endemic” areas haven’t built up immunity to the parasite, and commonly present with more complicated forms of malaria later in life. (HIV can be associated with more severe malaria as well: all 3 in these vignettes were HIV-tested, and all were negative.) Of note, all were afebrile on initial presentation, as are up to 40% of patients with cerebral malaria.*

*Although impossible to be sure without EEG confirmation, all probably had malaria-induced NCSE as the proximate cause of behavioral change. Since by definition cerebral malaria itself causes “encephalopathy” (via CNS arteriolar sludging and ischemia, cytokine effects and/or edema), in each of these cases there were clinical clues to suggest that the CM-encephalopathy was probably being mediated through “complex partial status epilepticus, CPSE”.*

*- Patient a) was fully alert and hypervigilant with diffusely increased muscle tone, but totally mute and unable to understand or follow commands. He probably was*

*aphasic (although couldn't be fully evaluated for it); he was staring, and blinking more than usual - thus subtle motor findings.*

*- Patient b) exhibited strange behavior for nearly 2 weeks. Auditory hallucinations are seen in schizophrenia, ictal psychosis and encephalopathy so they do not help differentiate much, except that in schizophrenia they are often centered around the patient, and in the other forms not necessarily so – in this case they weren't. This patient exhibited repeated reactive behavior (wandering around town), and carried the fearful panicky expression described in absence SE. Most notably, his mental status fluctuated unpredictably and erratically within seconds to minutes for 3 days prior to diagnosis; and he manifested a brief convulsive seizure prior to the start of appropriate therapy for CM.*

*- Patient c) exhibited both stereotyped and reactive automatisms in a classic repetitious pattern on admission – his was the most overt example of hyper-vigilant, staring, bizarre CPSE.*

**8. Patient (c) was given treatment for both diagnostic suspicions, and the next morning and throughout much of the next day, was comatose, unresponsive to pain. On exam there were no hand, finger, or eyelid twitches seen; he had roving, dysconjugate eye movements; PERRLA, doll's eyes intact.**

**What is the differential diagnosis of the prolonged coma and the most likely cause?**

- *NCSE with coma*
- *Cerebral malaria without NCSE*
- *Hypoglycemia due to malaria/IV Quinine*
- *Effect of benzodiazepines*
- *Prolonged post-ictal state*

*Since the coma started after diazepam was given (2 doses, 10 mg IV each, 30 minutes apart) and IV quinine administered, it is improbable that NSCE would worsen with therapy, or that CM would become even more pronounced and deeper resulting in coma. Hypoglycemia, a complication of both malaria and quinine therapy, can be (and was) ruled out by checking finger stick glucose. (If that wasn't available, IV glucose as an empiric trial would have been appropriate.)*

*The coma was probably an effect of the benzodiazepine therapy, possibly compounded by an unusually prolonged post-ictal state.*

**9. Patient (c) woke up sometime the following night, and in the morning seemed fine. His (loyal) friends and family had kept the vigil, and were obviously relieved and happy.**

*The next day however, he began seeing out the window a procession of people and strange animals walking across the roof of the adjacent ward. He was overtly animated, and described each one vividly and addressed them verbally....*

**What might have been happening?**

- *First diagnosis was wrong: maybe he is schizophrenic with a false positive paracheck, i.e. the malarial parasite not causing the problem, but circulating in his bloodstream. However, he was febrile later the night of admission, and given the pretest probability of CM as the root cause of his (obvious) NCSE, it's quite likely that the malaria diagnosed is indeed causally related and that his behavior was seizure-related. Furthermore, his friends and family were again adamant that they had never witnessed any unusual behavior whatsoever in the past.*
- *Recurrent CM-induced NCSE, this time with visual hallucinations rather than automatisms. Possible, but by this time he had been on IV quinine for >48 hours. Why now? (His glucose was rechecked, normal.)*
- ***Post-ictal psychosis:** Psychosis may develop following either generalized or complex partial seizures, usually after a prolonged seizure and a lucid interval of anywhere from a few hours to a month. Hallucinations are common, usually visual but sometimes multi-modal, as are paranoid delusions. Full recovery is usual.*

*This was thought to be post-ictal psychosis. The treatment for CM was continued, and he fully recovered.*

### **Suggested Reading:**

- Kaplan, P. and Fisher, R. Imitators of Epilepsy Chapters 4, 8, 20; Demos, 2nd Edition  
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