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 Katherine Unger at 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 44 – Bizarre and Treatable x 5

Read the following case vignettes and identify the diagnostic theme common to them.

a. A 15 year old boy returns from 3 months in Rwanda, confused and combative. He went to Rwanda from Kisoro when his family heard about the death of his grandmother to claim their inherited land. When he arrived, he discovered squatters living on the land and (according to family members now with him at the hospital) fought with them, ultimately threatening them with his machete. For this threat, in Rwanda (!), he was arrested and jailed for 2 months. He was released about 2 wks ago, made his way to Kisoro and has since been "crazy": confused and violent, stopping cars in the middle of the street, not making any sense, destroying the furniture in his house. He was finally brought to the hospital.
He never acted like this before and had done well in school.

On exam, he was hyper-vigilant, combative, generally uncooperative, and afebrile with normal vital signs. His lymph nodes, lungs, heart, abdomen were normal with the exception of splenomegaly, 3 cm below the costal margin. He walked with a limp, but hip, knee and feet appeared normal with only tenderness elicited on deep palpation under right plantar arch.

b. A 46 y/o male had fever, vomiting and headache about 2 weeks ago for which he took "malaria pills" for 3 days, felt somewhat better and returned to work for 4 days. About 5 days prior to admission, he again had a headache with chills for a day and went to bed. According to his family, he slept "all the time" for 2 days without eating, and got out of bed yesterday for the first time. He was confused, didn't recognize family members consistently and was brought to the hospital.
On direct questioning, his family noted he had vomited a few times, and had a mild non-productive cough. He had never been confused before.
On exam he was afebrile, seemed relaxed, and identified his wife and family members easily. Physical exam uncovered no abnormalities; his neuro exam was non-focal; on gross mental status evaluation he couldn't remember the month although he remembered the year.

Three hours later however, his wife calls you over. He appears easily distracted and thinks he's at home in 1980. He recognizes his wife as someone he knows, but thinks she is his cousin from Kampala. He seems quite anxious, thinking the nurse is out to hurt him.

c. **A** 20 y/o male went to Kampala about 6 months ago. According to friends there he was well until 7-10 days ago when he began complaining of fever and abdominal pain. He was treated for malaria with fansidar for 2 days, seemed better but then began acting strange. A diagnosis of meningitis was made (no LP done) and treatment was switched to antibiotics. He continued to act "strange" and on day 3 of therapy, since his friends couldn't miss any more days of "digging" (farming) to attend him in the hospital, they put him on the bus for Kisoro and family. When he arrived, he was quiet and withdrawn, not eating and "not himself" for 3 days at home. He had never acted strange like this before and family brought him to Kisoro District Hospital.

On physical exam he was afebrile and vital signs were normal. He lay motionless and then suddenly jumped away when approached, screaming and terrified when touched (by "Mzungo" (white) physicians). For 2 days he remained withdrawn, and intermittently and unpredictably aggressive. He had no apparent photophobia and was moving his neck freely. A rapid HIV test was negative. In the middle of the 3rd hospital night, he seized.

d. 49 y/o male brought to the hospital by his family because he has been acting strangely for the past 2 months. Previously in fine health and "good" with his family, he began acting inappropriately with occasional violent outbursts. Last week at home he was found burning his clothes, and over the past few days this poor subsistence farmer from a village without electricity or running water was obsessed with finding (and demanding!) his computer. He has not been eating normally and has lost some weight.

Physical exam is unremarkable without fever, lymphadenopathy, hepato-splenomegaly, neurologic focality or cardio-pulmonary findings.

e. 29 y/o mother of 4 is admitted with 3 months of cough, sputum, fevers, and marked weight loss of more than 12-15 kilograms. Exam is notable for severe cachexia, a weight of 38 kg,

crackles in right upper lung field posteriorly. AFB is (+), HIV negative. She is started on RIPE (rifampin, INH, PZA, and ethambutol). By the third day, she feels stronger and begins to ambulate. On the 4th day she thinks the nurse is trying to kill her and the next day, she is disoriented and combative, yelling and needing to be restrained by family. On exam she is afebrile with a supple neck, grossly non-focal; disoriented, and hyper-vigilant.

1. What do most these presentations have in common?

- *Change in mental status: organized, psychotic behavior*
- *No prior history of similar illness*
- *In 4 of the 5, the condition evolved over hours to days*
- *Afebrile, without focal or other neurological signs except mental status change*
- *All are caused by a (treatable) infection (!) or its therapy*

2. a) Four of the 5 are examples of which neurologic condition or state?
b) How is clinically defined?
c) How is it differentiated from psychosis?

a) Delirium

b) Delirium is defined by "CAM: Confusion Assessment Method" as 1 and 2 and either 3 or 4:

1. *acute change in mental status (over hours to days) which fluctuates (waxes-wanes) in severity during the day.*
2. *inattention: distractible, has problems keeping track or focusing*
3. *disorganized thinking: unclear or illogical or unpredictable or delusional, hallucinations, etc.*
4. *altered level of consciousness: either hyper-alert or hypo-alert (lethargic, stuporous, comatose)*

c) Delirium can mimic schizophrenia, mania or depression. The following clinical observations can help differentiate delirium from psychosis:

- *Psychosis is more likely to have preserved recent memory and orientation to time/place;*

- *Claims of being specific people (like Jesus) are more likely psychotic;*
- *Hallucinations in delirium are visual, or visual and auditory; schizophrenia more auditory.*
- *Psychosis can be acute too, but often with earlier episodes.*
- *Age: delirium more likely > 40 without prior psychiatric history*
- *Careful physical exam and vital signs – looking for signs of infection*
- *Delirium is more likely if there is decreased level of alertness*

3. What were the likely etiologies of each of the case vignette examples?

a. *Foot abscess,?malaria: In this boy, paracheck was (+) and cerebral malaria was initially diagnosed, although the time course of his bizarre behavior was long. However, the patient didn't respond to either coartem or quinine (the latter was given when he refused oral medications). His foot abscess later became obvious, explaining the observed limp, and was drained.*
Psychosis has also been reported as a post-malaria syndrome occurring 1-3 weeks after malaria, but is rare.

b. *Pneumococcal pneumonia: although initial PE was reported as (-), a more careful (or experienced) physical exam by the attending identified crackles and loud tubular breath sounds in the right axilla, illustrating the importance of a compulsive lung exam that includes the axillae. The new, "mild, unproductive" cough was the (unremarkable) clue in the history, and the vomiting and confusion were likely part of the sepsis syndrome. The patient later spiked a fever and responded to antibiotics.*

c. *Malaria: 1/3 of patients with cerebral malaria are afebrile at presentation; after this patient seized, he spiked a fever. Paracheck (malaria RDT) was (+), and he responded to quinine. In cerebral malaria, organized bizarre behavior can be caused by either the direct effect of the infection itself on the CNS mediated by cytokines, or by complex partial seizures ("temporal lobe epilepsy" or "non-convulsive status"). Seizure activity can be prolonged, recurrent and subtle, mimicking coma or behavior change. (N.B. Although malaria was the initial diagnosis in the other hospital, he was treated with a drug to which there's at least 20-30% resistance. He was clearly resistant to it. His mental status change, a manifestation of cerebral involvement by malaria, was then interpreted as "meningitis".)*

d. *HIV: This is the one, more chronic presentation of psychotic behavior in these 5 vignettes – going on for 2 months in a 49 year old. Check the HIV status. CNS HIV can present as psychosis, catatonic schizophrenia (!), movement disorders, etc. One must have a low level of suspicion for rare/unusual presentations of "common" Ugandan*

diseases like HIV, especially when the presentation is atypical in some way (e.g. age of onset) for the prototype disease it can mimic (e.g. schizophrenia in this case).

e. *Drug toxicity: anti-TB drugs. Psychosis is a side effect of ethambutol, PZA and INH (!). These drugs are provided in fixed combinations (RIPE) and in standard "adult" doses – often to very underweight patients who then manifest CNS effects as drug levels surpass the toxic level for a cachectic patient.*
Stop all drugs. When stable, recalculate dosing and decrease the dose of the main potential culprits like ethambutol. Monitor as treatment is re-initiated, and increase dose as patient gains weight.

Infection is thought to provoke delirium through activation of CNS microglia by pro-inflammatory cytokines (interleukin 1b and 6, and TNF alpha) generated in the periphery. The microglia then amplify the response in the CNS - where cytokines reach high levels that persist for long periods. This amplification cycle is particularly robust in adults. The cytokine-induced neuro-inflammatory response is ultimately toxic, causing neuronal loss and signal transmission abnormalities which result in behavioral change. In older adults, the prolonged neuro-inflammation is hypothesized to cause the dementia that oftentimes later complicates delirium.

Other causes of delirium in Africa include other infections common on the continent (typhoid, leptospirosis, borrelia, etc.), drug toxicity and withdrawal from drugs, and metabolic problems that are often difficult to diagnose without labs, like hypercalcemia and hyponatremia. It's always important to inquire about drugs the patient has taken, and ask the patient and the family about alcohol. N.B. In patients recently started on medications, the drugs are prime candidates - even if the behavioral side effect is reported to be rare!

Remember, sedation is dangerous if hypoxemia is present, so check pulse-oximetry. Also check the finger-stick for hypoglycemia; smell the patient's breath for the musty odor of uremia; and look carefully for stigmata of liver disease, signs of hyper/hypothyroidism and clues to pre-existing Addison's. Chronic disease often goes undiagnosed for years, and patients present with florid end-stage complications rarely seen in the West these days.

Suggested Readings:

Inouye SK, et al Clarifying confusion. Ann Intern Med. 1990;113(12):941-948.
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Van Gool W, et al. Systemic infection and delirium: when cytokines and acetylcholine collide Lancet 2010; 375: 773–75