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 51 – Headache and Confusion

A 50 year old woman presents with increasing headache over 5 days and confusion for two days.

Hypertension was first noted 2 years ago when she suddenly lost vision in both eyes. In the hospital she recalls her blood pressure (BP) was "very high" although the records couldn't be located. She left the hospital on unknown medications after about a week. Although she regained some vision over time, she can no longer work as a seamstress. She attended the Chronic Care Clinic in Kisoro District Hospital for 2 months and then stopped coming because of distance, and presently she is not on medications for hypertension. Her HIV test was negative.

The headache was noted upon awakening 5 days ago and has slowly worsened since, although it seems to wax and wane. It is partially relieved by the ibuprofen she's been taking for the past 3 days. Her daughter says she has seemed a bit confused for the past 2 days, making non-sense remarks and laughing.

There is an unclear history of possible loss of consciousness about 3-4 years ago, but no prior history of headaches, transient loss of motor or sensory function, or chest pain. She has had no fever. Her father died with "swollen legs", her mother suddenly at age 65, and her 3 siblings are alive and living in Kampala. She's unaware of their medical history.

Physical Exam: In no distress, sitting in bed, well-nourished.

BP 240/190 right, 220/175 left; 5 min 200/160 right; 30 min 190/150 right; HR 70; T 97;

Eyes: no cataracts; acuity hard to measure due to difficulty understanding but seems poor
fundi: No papilledema appreciated, discs flat bilaterally; A/V ~0.4; increased tortuosity, ⊕ A/V nicking;
Left eye: flame hemorrhage, 1 disc distance, at 2:00; scattered hard exudates around macula on left;
Right eye: 2 dot hemorrhages, 4 and 7:00, ~ 2 disc diameters from disc; soft exudates at 11:00, 1 disc diameter from disc, ½ disc diameter in size;
mouth: no tooth tenderness to percussion, no thrush;
face: no sinus tenderness to percussion/palpation
Neck: no JVP or HJR; neck supple with full ROM; no LAD
Lungs: clear
Heart: sustained LV PMI/heave, ~ 2-3cm diameter, 5th ICS, 1 cm lateral to MCL;
loud S_4; "triple sound" ~S_1 heard in 4th ICS medial to MCL;
Gr1/6 short systolic ejection murmur;
Abdomen: no hepato-splenomegaly, tenderness or masses; rectal: brown stool, guaiac (-).
Extremities; pulses +2, no skin lesions, nails normal
Neurologic: Mental Status: looks distracted, oriented to name, place, but not month;
CN: intact, except bilateral visual acuity poor as noted;
Motor, Sensory, Cerebellum, Gait: normal
Reflexes: +2 throughout, except +3 knee jerks and ankle myoclonus bilaterally

1. **What is the probable (and most worrisome) diagnosis in this patient?**
   What is its pathogenesis?
   What else is in the differential and why are these less likely?

   - *Hypertensive crisis with headache due to cerebral edema is the most likely diagnosis.*

   - *Although its pathogenesis is not understood entirely, hypertensive encephalopathy is characterized by headache, altered mental status, visual impairment, seizures, and fluctuating neurologic signs. These are caused by luminal narrowing and vasospasm with micro-thrombi and ischemia, and/or failure of microvascular autoregulation at very high blood pressures leading to hyperperfusion of capillary beds and cerebral edema.*

   - *Other possibilities include other causes of new-onset progressive headache in a patient with essential hypertension - with pain acutely raising the blood pressure.*

     Etiologies of progressive headache include new-onset migraine (with "status migrainosis"), hypertensive cerebral hemorrhage, mass lesion (e.g. tumor or abscess), and chronic meningitis such as TB or Cryptococcus.
     Pain or acute anxiety can raise blood pressure, particularly in hypertensive patients, and increased intra-cranial pressure can induce hypertension (and often bradycardia). Ibuprofen and other NSAIDS also raise blood pressure through salt retention and blocking the local renal effects of vasodilating prostaglandins.
     These are all unlikely as the primary cause of this patient's headache for many reasons: She's HIV-negative (as of 2 years ago); has no prior history of headaches; and is afebrile and without focal findings on neurologic exam. The ibuprofen was taken for the headache and didn't precede it.
     Furthermore, the sheer severity of the hypertension and the hemorrhages on funduscopic exam support the diagnosis of an early hypertensive emergency (despite the absence of papilledema).

   - *Hypertension (HT) is usually asymptomatic (although headaches are somewhat more common in patients with DBP > 110). Most associations of HT with headache are due to "detection bias" – the patient presents to medical attention with a headache (unrelated to the blood pressure), and HT is noted incidentally. The HT is then "diagnosed" as causing the headache.*
     Doctors can inadvertently cause harm to patients by associating HT with symptoms, particularly headache, by leading to non-adherence with anti-hypertensive therapy when the patient is feeling well.

2. a) What differentiates "malignant" vs. "accelerated" hypertension, and a hypertensive "emergency" vs. "urgency"?
   b) How would this patient be classified?

c) What utility do these classifications hold, and what observations need to be made for a complete assessment?

- *Evidence of end-organ damage, particularly papilledema, has defined malignant hypertension - a syndrome of vascular damage associated with severe elevations of blood pressure, usually diastolic BPs >140 (but if acute, can be much lower, ~110). "Accelerated" HT is malignant-range HT without papilledema.*
  However, since papilledema is an exam finding with considerable inter-observer variability and physical exam skills are in short supply nowadays, "malignant HT" usually refers to HT with evidence of acute end-organ damage, and "accelerated" HT, malignant-range BP without evidence of acute vascular damage.

- *Hypertensive emergencies include severe hypertension with encephalopathy, acute renal failure, stroke, pulmonary edema, and dissecting aneurysm – all complications of the elevated blood pressure which needs <u>immediate</u> treatment, while "urgencies" include hypertension with LV failure, unstable angina, or severe BP elevations (DBP>140) without symptoms. While prompt effective treatment is important in "urgencies", it needn't be within minutes but rather hours, or in the case of the asymptomatic patient, within days. Most with asymptomatic malignant-range BP without evidence of end-organ damage will stay that way for months to years (as did Franklin Delano Roosevelt during the last 2-3 years of his presidency during which his BP was repeatedly documented to be >220/120-140).*

- *In this patient, the fundoscopic findings of soft exudates (see below) and hemorrhages corroborate the less specific clinical diagnosis of hypertensive encephalopathy, based on progressive headache and mental status change, and make this patient's presentation an "emergency" – i.e. malignant hypertension.*

- *These classifications are useful prognostically (e.g. >80% with untreated malignant HT are dead within a year) and therapeutically, re-rapidity of treatment.*

  Most of the criteria are clinical, except renal failure:
  Encephalopathy – headache, mental status, fluctuating focality on neurological exam;
  Stroke – focal neurologic symptoms and signs;
  Pulmonary Edema – acute respiratory distress with rales;
  Dissecting aneurysm – severe chest-back pain often with BP difference between arms;
  Renal failure usually requires laboratory testing: a urinalysis – looking for red blood cells/proteinuria as evidence of acute damage, and creatinine if available.

3. What is the significance of the following PE findings?

- **BP difference of 10-20/15-20 between arms:**
  A difference of this magnitude without symptoms is not clinically significant and not reproducible. In one recent large study, differences of < ~ 40 were not reproducible. In absence of a history suggesting aortic dissection, differences > 40 were most often due to

different degrees of atherosclerotic involvement of the subclavian arteries. (It's probably best to go by the arm with the higher BP in any case.)

- **BP falling with successive measurements:**
  Clinically significant BP variability even within an office visit, is common, seen in 10-20% of measurements, and greater with higher BPs. Because of this, the actual BP measure to record and make decisions by is the average of a series of 2-3 BP's taken minutes apart while the patient is seated and relaxed.
  Stress and strange environments, which the hospital certainly qualifies as, adds another artifact to the measure of BP in this patient. (In one study in Italy, the doctors arrival at the bedside of hypertensive patients induced a rise in BP of >50/25, which dropped significantly after 2-3 minutes.)

- **normal teeth, sinuses**
  Should always be checked on exam in patients with headache by tapping/percussion. Pain originating from the teeth or sinuses can exacerbate existing hypertension.

- **fundi:**
  The hemorrhages and exudates seen in this patient are categorized as "Grade 3" changes according to the Keith-Wegener-Barker classification, far more severe and less common than the vasospastic changes of Grade 1, or the arteriolar sclerotic changes of Grade 2. Grade 3 changes indicate accelerating acute end-organ damage: retinal changes reflect similar pathology in the brain parenchyma.
  - *flame hemorrhages radiate from the disk, are located in the superficial retina;*
  - *soft exudates, or cotton-wool spots, are signs of ischemic edema of the retina;*
  - *hard exudates reflect deposition of lipoprotein from earlier capillary extravasation, are "healing" and more benign;*
  - *A/V~0.4, tortuosity, and "nicking" - signs of significant arteriolar sclerosis, Grade 2 changes. The normal A/V (ratio of widths of the arteriolar and venous lumens) is ~0.8, and it decreases with arteriolar sclerotic changes in the walls of the vessels.*

- **PMI: sustained LV PMI/heave, ~ 2-3cm diameter, 5th ICS, 1 cm lateral to MCL**
  Sustained means > ½ systole and the minimally displaced (but forceful) "heave" is consistent with concentric hypertrophy of the myocardium due to afterload stress - as in hypertensive cardiomyopathy or aortic stenosis.

- **loud S_4; triple S_1 heard in 4th ICS medial to MCL**
  The loud S_4 stems from a vigorous atrial contraction ejecting blood into a non-compliant hypertrophied ventricle.
  The "triple S_1" is the sound usually caused by the S_4, M_1 (mitral closure), and aortic EC (ejection click).
  (The EC is often heard in adults with HT, the third component of the normal S2 (M1-T1-EC), and often heard better than T1, silent in this case).

- **Neurologic exam: orientation and lack of focality**

The exam is remarkable for 2 things: a mental status (in a 50 year old) which is "off" and oriented to only name and place, not time. This corroborates her daughter's observation of slight confusion over the past 2 days.
And lack of definite focality - which suggests that the progressive headache is not due to an intra-cerebral hemorrhage/stroke, another potential complication of the severe hypertension, but rather to the diffuse "capillary leakage" that characterizes hypertensive encephalopathy.

4. Which tests, available in most district hospitals in rural Africa, should be requested and why?
How would you interpret their results in this patient?

- urinalysis: an active sediment with red cells and proteinuria will help diagnose acute renal involvement with "fibrinoid necrosis" of small vessels, often seen in hypertensive crises. In most cases of hypertensive encephalopathy there is some degree of pre-existing chronic renal insufficiency, and often acute renal failure is superimposed. When simultaneously discovered, it's often impossible to tell whether the hypertension is due to or caused the renal disease (glomerulonephritis).
- hematocrit: although often multifactorial, anemia could indicate underlying renal insufficiency, and absence of anemia, might suggest (weakly) normal renal function. Furthermore, malignant hypertension is associated with an acute microangiopathic hemolytic anemia.
- EKG: chronic severe hypertension, especially of this degree, is usually accompanied by EKG signs of left ventricular hypertrophy (LVH). Absence of LVH suggests acute elevations in blood pressure (less than months' duration) as in acute glomerulonephritis or pre-eclampsia. In our patient, with a history of a prior hospital admission with severe hypertension (and visual loss), we know the hypertension is "chronic". However the EKG is still useful: increased electrical voltage alone is a sign of myocardial muscle hypertrophy, whereas ST depressions with T wave inversions, or "repolarization abnormalities", indicate underlying myocardial fibrosis; and Q waves indicate prior subclinical infarction (although Q waves in V1-3 may be seen in severe LVH hypertrophy).
- creatinine: unavailable

In this patient,
- the urinalysis demonstrated many RBCs, no casts, and +2-3 proteinuria on dipstick with s.g. 1.020.
- the spun hematocrit was 32, and a smear showed normochromic, normocytic RBCs without evidence of fragmentation.
- EKG showed marked LVH with ST/T wave changes but no abnormal Q waves.

Interpretation:
There is no evidence of hemolysis, but the active sediment suggests some degree of acute renal insufficiency due to fibrinoid necrosis of small vessels (which is partially reversible with control of HT).

The anemia however suggests an element of chronic renal insufficiency as well (with vascular myointimal proliferation and "onion-skinning" leading to sclerotic glomeruli) - as expected against the background of hypertensive encephalopathy.

5. How would you treat this patient?
What short-term adverse effect can be expected with successful therapy?

This patient should be treated with the proverbial "kitchen sink"! (aiming for a 25% reduction in BP over 24 hours, not more lest cerebral perfusion is impaired).

In the West, this patient - with evidence of acute retinal, cerebral and probably renal involvement by malignant hypertension - would be in an ICU being treated with a nitroprusside drip to lower BP immediately.

In a rural district hospital in Uganda, the theoretical approach is similar: lower blood pressure aggressively – in this case, with whatever oral medications with different/complementary mechanisms of action can be found in the hospital pharmacy. These are usually oral medications with a slower onset of action than parenteral drugs. Multiple medications but at their usual initial doses should be begun, rechecking in 6-12 hours and increasing doses gradually. Aim for a 25% reduction in BP in the first 24 hours, and try not to overshoot.

ACE-inhibitors should be used since malignant hypertension is a high-renin, high-aldosterone state (that despite some degree of renal insufficiency) is often associated with hypokalemia.
Calcium channel agents, particularly dihydropyridines like nifedipine or direct vasodilators like hydralazine, should be added as well.
Diuretics, probably furosemide, will be necessary, especially if there's renal insufficiency - but even if not, as a necessary component of a long-term multi-drug regimen.
Beta-blockers should be administered. Even though less efficacious than calcium channel agents or diuretics in blacks (in the U.S.), they are available and inexpensive in Africa and will help control the BP over the short term and limit reflex tachycardia from vasodilators. (If the BP is controlled and step-down is later indicated, B-blockers would be the first to go.)

As the BP and renal perfusion pressure drop, renal function may deteriorate in the short term. However, long term maintenance of lower blood pressure over the succeeding months allows the fibrinoid necrosis and renal edema to resolve and renal function to improve somewhat.

6. Why "hypertension in Uganda"?
What additional social considerations apply to hypertension in Africa?

- *Although considered a disease of "modern life", hypertension has always been with us. Urbanization and sedentary lifestyle with obesity increase the phenotypic expression of hypertensive genes (or an unfavorable fetal environment), but hypertensive complications are a major cause of morbidity and death in the rural developing world as well, especially because it's undetected and untreated. The development of hypertension has*

been inversely correlated with birth weight in many epidemiologic studies, presumably mediated by fewer nephrons at birth with decreased ability to excrete salt. This initiates a physiologic cycle leading to increased peripheral vascular resistance and hypertension. The Third World bears about 65% of the total cardiovascular deaths in the world, where stroke and MI are the leading causes of death at present. In rural regions, although ischemic heart disease is much less frequent than in urban areas, hypertension is a common cause of heart failure, renal failure and stroke. Cerebral hemorrhage from untreated hypertension causes nearly half of strokes in the Third World vs. 10% in the West.

- *Although malignant hypertension is rare in the West at present, in one hospital based series from South Africa in 1990, 57% of those with essential hypertension presented with malignant hypertension due to late presentation of previously undiagnosed disease and the co-existing high incidence of renal impairment. (J Hum Hypertens 1990; 4: 379)*

- *In the Kisoro district of SW Uganda, one comprehensive door-to-door screening of 130 asymptomatic adults in the rural village of Gakoro detected BP > 180/115 in 2 of them: perhaps a low prevalence, but …*

- *HT is undiagnosed, untreated and unaffordable in most settings in the world in which patients*
  a) must pay for medications and
  b) make less than $10 a week.

Lack of education, understanding, access, money and symptoms lead to poor adherence - as with this patient who had already suffered a prior stroke and incomplete cortical blindness. On day 3, with her blood pressure still very elevated but feeling better, she "eloped" home with her family in the middle of the night, without medications.

Suggested Readings:

Ibrahim MM, Damasceno A. Hypertension in developing countries Lancet 2012; 380: 611–19

de-Graft Aikins A, et al., Tackling Africa's chronic disease burden: from the local to the global Globalization and Health 2010, 6:5

Opie L, Seedat Y Hypertension in Sub-Saharan African Populations Circulation. 2005;112:3562-3568

Kaplan N Malignant hypertension and hypertensive encephalopathy in adults UpToDate 2013

Kaplan N Treatment of specific hypertensive emergencies UpToDate 2013

McGee, Steven, *Evidence Based Physical Diagnosis* 2nd Edition, 2007, Saunders/Elsevier