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RETURN SERVICE REQUESTED

BEWARE MALIGNANT ARRHTHYMIAS WITH QT ELONGATION

An interesting clinical vignette from Proietti et al, *Ann LongTerm Care*, 2011, reminds us of the propensity to QT prolongation and *torsades de pointes* with fluoroquinolone antibiotics in the predisposed. Fluoroquinolones are extremely lipophilic (hence able to penetrate tissue) and uniformly effective against gram-positive/gram-negative microbes, making them antibiotics of choice for several clinical infections. Quinolones also prolong cardiac repolarization, presumably through a dose-dependent blockade of K efflux channels, a feature thought to be mediated by substitution at the 5-position of the fluoroquinolone ring (proton radicals at that position tend to reduce the effect on QT, whilst methyl/amino group substitution increases QT interval). Therefore, moxifloxacin has the highest risk of QT prolongation, whilst ciprofloxacin has the lowest risk; all other fluoroquinolones are intermediate in risk. Risk factors for QT prolongation include: old age > 65 y.o., female gender, underlying structural heart disease, ischemic heart disease, paroxysmal tachyarrhythmias (including atrial fibrillation), genetic long-QT syndromes (typically from ion channel mutations or polymorphisms), concurrent use of other QT-modifying medications (particularly macrolide antibiotics and Bactrim/Septra and class III anti-arrhythmic drugs), and to a lesser extent, presence of clinical hypertension, history of diabetes mellitus, polypharmacy (with agents that affect metabolism or elimination of fluoroquinolones or other QT-prolonging drugs), chronic kidney disease, hepatic failure, inotropic drug therapy (especially with dopamine/dobutamine), electrolyte disorders (especially hypokalemia, hypocalcemia and hypomagnesemia). Other QT-prolonging medications of clinical importance include amiodarone, anti-cholinergics (phenothiazines/anti-histamines/anti-psychotics), methadone, QPD antiarrhythmics (quinidine, procainamide, disopyramide).

NOT TO BE MISSED: NEUROLEPTIC MALIGNANT SYNDROME (NMS)

Altered mental status from NMS in a patient on neuroleptic or dopaminergic medications, especially haloperidol and/or chlorpromazine, may be wrongly attributed to the underlying mental illness. Similarly, "sepsis without infection" following long-term neuroleptic treatment or sudden reduction in dose of dopaminergic drugs (such as levodopa) may be another pointer to evolving neuroleptic malignant syndrome; confusingly, anti-dopaminergic drugs (e.g. metoclopramide) and even drugs with neither dopaminergic nor anti-cholinergic effects (e.g. lithium, reserpine) may be associated with NMS. Always consider NMS in any patient on antipsychotic drug therapy presenting with DADDY FEVERS: Dopaminergic blockade (i.e. pseudoparkinsonism or pseudodementia), Acidosis, Diaphoresis, Delirium, Y chromosome (more common in young adult males), Fever/chills, Encephalopathy, Vital sign instability (from accelerated hypertension to refractory hypotension), Elevated muscle enzymes (CPK and aldolase), Rigidity and Septoid clinical picture (including hyperpyrexia and leucocytosis). NMS is life-threatening and must be treated as a medical emergency: stop all suspect medication(s), institute supportive care, address hyperthermia with cooling blankets, transfer to ICU (hemodynamic as well as ventilatory support may be needed), begin aggressive IV hydration with bicarbonate supplementation, administer benzodiazepines PRN for agitation, consider dantrolene/bromocriptine in serious cases. NMS must be differentiated from serotonin syndrome (SS) which bears a superficial resemblance to it, but NMS is an idiosyncratic reaction whilst serotonin syndrome is a predictable toxidrome resulting from excessive serotoninergic activation in the brain and elsewhere. NMS evolves slowly, but SS has an acute onset. Also, whilst the NMS patient is typically "still" with parkinsonic lead-pipe rigidity, the SS patient may be described as "hyperactive" with clonus. SS manifests as tremor/hyper-reflexia, akathisia/hyperkinesia and clonus (spontaneous or induced, ocular or peripheral). SS results from use of anti-depressants (especially SSRIs and MAOIs), opiate drugs (including Ultram/tramadol), anti-migraine triptans, psychedelic drugs such as LSD, CNS stimulants (including Ecstacy/MDMA, amphetamines and cocaine), and of increasing clinical importance, the following newer agents: phentermine/sibutramine, ritonavir, linezolid, Zofran/odansentron, Reglan/metoclopramide, risperidone, St. John's wort and yohimbine.

the SECOND OPINION

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FROM THE EDITOR

I never particularly cared about the now-infamous (and mercifully retired) Don't Ask, Don't Tell policy of the Clinton era, not so much because I was largely indifferent to the goings-on between consenting adults ensconced in the privacy of their homes, but because it allowed official hypocrisy to pass off as executive doctrine. When open discussion is subverted or otherwise discouraged, all manner of subterranean interference and gamine overreach is assured: therein lies the foundation of conspiracy theories, where adults regress into a world of Dickensenian make-believe. And there are multiple examples of this, from the childhood fable of the Emperor's New Clothes through the military decapitation of Hannibal's Carthage during the Third Punic War to Saddam Hussein's delusional insistence that Baghdad was inviolate, despite all evidence to the contrary. When there is nobody left to speak truth to power, power becomes its own truth. *Carthago delenda est.*

Who is scared of gays- or of the medical autopsy? A generation ago, medical autopsies (a.k.a. postmortem examinations) were *de rigueur*, an obligatory end-piece to unexpected death. It was our professional housekeeping tool, which uniformly informed and humbled all physicians, as we came to learn from our mistakes before we buried them. It was our last homily to those who died under our care, coda to our life-long professional ministrations unto death. The benefits were well recognized: it helped with our teaching and learning, opening up unexpected reserves of uncertainty and wooly diagnostic thinking; it was a tool both for research and demonstration, mesmerizing countless generations of greenhorn medical students; it allowed for tissue harvesting, including hormone elaboration and pituitary glands in days of yore; but above all, it put the lie on the certainty- and efficiency- of our daily professional work, quietly pointing out the sodden areas of our collective ignorance. The findings of the medical autopsy was the gold standard to which we aspired. It made us all better doctors.

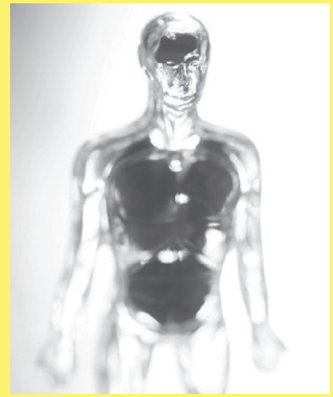
Why then, is the autopsy a dying art? What has caused us to distance ourselves from that which, presumably, made us whole? These days, if you want to view an autopsy, watch CSI: Miami or similar fare. Nobody knows for sure why the autopsy is dying, and those who might have a better insight- those denizens of formaldehyde-proof rooms in hospital basements- are simply not talking. I just know that we very seldom perform autopsies here in Athens- or Atlanta, Augusta, even Boston- for that matter. Senior doctors were always ambivalent about the findings from autopsies, which often revealed that our gods of the Grand Rounds usually had feet of clay. Others were concerned about providing further ammunition- as if they needed any encouragement- to malpractice attorneys. It did not help that the Joint Commission (JCAHO) in its ponderous wisdom, had dropped the requirement for accredited healthcare facilities to maintain a 20-25% autopsy rate. Insurers and other third-party payers were reluctant to fund the "extraneous" activity of post-mortem examination; hospitals proved unready or unwilling to bridge the funding gap. That unfortunate task fell sometimes to bereaved families, who often felt doubly victimized that on losing a loved one, they also had to pay to ascertain the doctors' errors. Little wonder that family-sponsored autopsies were often a prelude to medical malpractice assertions.

Recently, the virtual autopsy, a.k.a. virtopsy, has been advanced as a worthy replacement for the medical autopsy: it was clean, no cadaver disfigurement here, and could be done without anyone being the wiser. It is still unclear to me why a public testament to scientific rigor such as a timely medical autopsy, should be done under the cloak of darkness. All the same, the virtopsy concept has been adopted in most of Nordic Europe and within the US military, where high-resolution CT images are followed by limited biopsies of abnormal tissue. A recent study from the venerable John Radcliffe Hospital, Oxford, suggests that doctors still miss 40% of the causes of death in our patients, and the virtopsy (using both CT and MRI) was only accurate about half the time, the CT alone in 42% of cases and MRI alone in 32% of cases. Interestingly, Wichmann's study in Annals of Internal Medicine last month showed that whilst medical autopsies might miss traumatic fractures and pneumothoraces, the virtopsy was more likely to miss cardiovascular disease and cancer as causes of death.

And what, after all, are our obligations to our dead patients? We owe them- and their families- a true explanation of why and how they died. No more, no less. We cannot achieve that goal without autopsies.

I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, Ph.D, FACP



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PREDICTING CORONARY STENT THROMBOSIS DESPITE DUAL ANTI-PLATELET THERAPY

Dual anti-platelet treatment with ASA and Plavix reduces post-stent thrombosis after coronary angiography by at least 80%. Yet, when it occurs, post-stent thrombosis is a harbinger of sudden cardiac death or devastating (and often recurrent) myocardial infarction in most survivors. Cayla et al, *JAMA*, 2011, attempt to define clinical predictors of post-stent thrombosis: gene variants, clinical features and angiographic characteristics. Adding to previously known risk factors such as presence of diabetes mellitus, under-sized or under-expanded stent fit, bifurcated or complex angiographic lesions, coronary artery dissection during stent deployment, and the most common underlying factor, interruption or non-compliance with dual anti-platelet therapy, we can now add cytochrome CYP2C19 status and other genes (such as ABCB1 3435 TT genotype and ITGB3 PLA2 carriage) where gene polymorphisms have previously been identified as risk factors for reduced platelet responsiveness to Plavix, performance of coronary stent/angiography in the acute setting, LV ejection fraction under 40%, concurrent use of proton pump inhibitors and higher loading doses of Plavix. Let the confirmatory clinical studies begin!

IS FOOD ADDICTION REAL? CAN IT EXPLAIN OBESITY?

Obesity is a common clinical challenge, and so far, medical science has no answer to this epidemic. It is thought that food addiction may play a role in development and maintenance of obesity, and tantalizing parallels have previously been drawn between substance abuse and food intake in obesity. Gearhardt et al, *Arch Gen Psych*, 2011, used functional magnetic resonance imaging of the brain to study neural activitation in obese and non-obese young women exposed to actual or anticipated "comfort foods", in this case, chocolate milkshakes. Subjects with high food addiction scores had greater neural activation of the anterior cingulate cortex, medial orbito-frontal cortex and amygdala in anticipation of food, as well as caudate nucleus and dorso-lateral prefrontal cortex, in close mimicry of the reward circuits activated in substance abuse. The interesting conclusion from these studies is that if similar mechanisms underlie both obesity and drug misuse, similar treatment models might prove rewarding in tackling both clinical problems.

EARLY NEPHROLOGY REFERRAL MAKES NO DIFFERENCE

The nephrology community has spent the last decade urging earlier referrals for chronic kidney disease; the tacit assumption was that early referral would translate to better outcomes. Not necessarily. Winkelmayer et al, *Arch Intern Med*, 2011, studied 323,977 older patients who recently initiated chronic dialysis for end-stage kidney failure. The findings were troubling: earlier referral has become more common, though not yet "standard of care" over the last decade; patients were started on dialysis with relatively higher residual kidney function as measured by estimated GFR; use of peritoneal dialysis was even lower than in previous years; crude 1-year mortality rate was unchanged by earlier referral. There was 1 positive finding, though: early referral was associated with a lower prevalence of anemia, a reflection of aggressive Procrit use in the pre-dialysis population. This study is clearly destined to be argued over and nitpicked by the nephrology community in coming years, though the bigger question will likely remain unanswered: would referral to specific nephrologists/practices make any difference?

HYPERAMMONEMIA: NOT ALWAYS FROM LIVER DISEASE

Blood ammonia levels are commonly requested in the work-up of suspected metabolic encephalopathy. However, an elevated ammonia level is a rather non-specific finding, and is in no way diagnostic of liver disease. Common causes of an elevated ammonia level are:

1. Prolonged tourniquet application during venipuncture or failure to transport blood sample on ice.
2. Bacterial overgrowth syndrome: chronic atrophic gastritis, long-term PPI use, et cetera.
3. Failure of hepatic metabolism of ammonia: fulminant liver failure, porto-systemic shunts (in cirrhosis), hepatic bypass, Reye syndrome.
4. Extreme exertion.
5. Inborn errors of urea metabolism & citrullinemia & severe zinc deficiency.
6. Valproic acid toxicity.
7. High protein meals.

FASCINOMA FROM THE ED: IS THIS LUMBAR STENOSIS?

A 74 y.o. gentleman with ESRD presented with mild dysphoria, low back pain and radiologic features of lumbar spinal canal narrowing on MRI. The (wrong) diagnosis of lumbar stenosis was made. Problem: cross-sectional spinal narrowing is critical but insufficient in making the diagnosis of lumbar stenosis (Suri et al, *JAMA*, 2010). This diagnosis requires both characteristic radiographic and clinical findings. The important clinical findings include: old age, typically >70 y.o.; bilateral buttock pain; typical stooped, wide-based stance associated with positive Romberg's test (a.k.a. pseudocerebellar syndrome); pseudoclaudication (a.k.a. neurogenic claudication) with pain (which may be associated with weakness, paresthesias) radiating down posterior aspect of lower limbs, and unlike vascular claudication, is improved (not worsened) on riding a bicycle (van Gelderen bicycle test); relief of pain on seating or bending forward or lying on side. Unlike most other causes of low back pain, medical treatment is often futile; surgery should be the primary intervention.

POOR TOLERANCE FOR LONG INTER-DIALYTIC DURATION IN ESRD

Despite the common finding of poor therapeutic compliance amongst dialysis patients (I once had a patient skip treatment for 2 months, only to be admitted to ARMC with uremic pericarditis and critical anemia!), even a 2-day break (as would occur over weekend transitions) is associated with worse outcomes. This finding is thought to reflect the limited homeostatic functional reserve of ESRD patients. Foley et al, *N Engl J Med*, 2011, studied 32,065 participants in the ESRD Clinical Performance Measures Project from 2004-2007. Medical occurrences were compared between normal weekdays and weekends When treatments were delayed for 2 days). All-cause mortality climbed from 18 deaths/100 person-years to 22.1 deaths/100 person-years, whilst cardiovascular events increased from 19.7 to 44.2, congestive heart failure from 16.9 to 29.9, acute MIs from 3.9 to 6.3, infection-related mortality from 2.1 to 2.5, strokes from 3.1 to 4.7 and dysrhythmias from 11 to 20.9. I think this is a message that every dialysis patient must hear.

LIES, DAMN LIES, STATISTICS: PHYSICIANS DON'T DO STATISTICS

Wegwarth et al, *Ann Intern Med*, 2012, surveyed a total of 412 primary care physicians over 2 years in 2 parallel groups. Each physician was presented with a hypothetical screening test supported by either irrelevant statistics or relevant statistical evidence. Remarkably, 69% of physicians thought the irrelevant statistical findings (e.g. increased 5-year survival following a screening test) were important, whilst only 23% appropriately weighted relevant statistical evidence. The study concludes that physicians who are often required to counsel patients on screening tests mostly do not have the statistical background to make appropriate recommendations. Well, well, well... the key thing is to remember that reduced mortality found through a randomized clinical trial is the only acceptable evidence for concluding that any screening test actually saves lives.

FOREIGN TRAVEL AND RELAPSE OF MULTIPLE SCLEROSIS

Yellow Fever vaccination with a live, attenuated virus (17D) is both relatively safe and effective, conferring immunity which lasts up to 10 years. Yellow fever is endemic in certain tropical nations, but requirements for immunization certificates by civil authorities often bear no direct relationship to disease transmission or risk. A self-controlled case study by Farez & Correale, *Arch Neurol*, 2011, demonstrated that vaccination was linked to exacerbation of clinical demyelinating disease in multiple sclerosis as well as significant rises in blood myelin basic protein as well as myelin oligodendrocyte glycoprotein and several cytokines (including interferons and complement proteins). Yellow fever is a potentially fatal infection, but travelers often receive vaccination even whilst visiting areas of little or no risk of virus transmission. The countries currently recommended by the WHO for yellow fever vaccination are: Angola, Argentina, Benin, Bolivia, Brazil, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Colombia, Congo, Ecuador, Equatorial Guinea, Ethiopia (not Eritrea), French Guiana, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Guyana, Kenya, Liberia, Mali, Mauritania, Niger, Nigeria, Panama, Paraguay, Peru, Rwanda, Senegal, Sierra Leone, Sudan, Suriname, Togo, Trinidad & Tobago, Uganda and Venezuela.

DRUG-RELATED ADVERSITY IS COMMON: BUT WHERE ARE THE CULPRITS?

The elderly are more likely to suffer from poor doctoring: they are more likely to visit (multiple) doctor offices, they have limited functional reserve, they tend to be more compliant with (unnecessary) medications, they trust their care-givers, and they (almost) never complain. The result is polypharmacy and a high rate of drug-related adversity. More than a third of the elderly are on 5-9 different pills, and at least 15% are estimated to regularly take 10 or more different prescription drugs daily! An estimated 100,000 elderly folk are hospitalized yearly in this country from drug-related health problems. Yet, our understanding of drug-related adversity in this vulnerable population remains rudimentary. The paper by Budnitz et al, *N Engl J Med*, 2011, tries to remedy that. First, the drugs implicated in drug-related hospitalizations are not the "high risk" drugs of Beer's lists, et cetera. It turns out that 33.3% of hospitalizations were from Coumadin; 13.9% from insulins; 13.3% from oral anti-platelet drugs (including ASA, NSAIDs and Plavix); 10.7% from oral hypoglycemic drugs, with a measly 28.8% attributed to all other medications. What could be done? First, recognize the vulnerability of our elderly population, and introduce new drugs with caution. Second, monitor INRs closely with concurrent medical illness or adjunctive drug therapy (coumadin is notorious for multiple drug-drug interactions) or change in diet; also consider switching to a direct thrombin inhibitor (such as Pradaxa) if cost is not an overriding concern. Be careful with all anti-platelet agents, especially in those with previous GI bleeds or concurrent gastrotoxic therapy. There is scarcely any compelling reason for long-term NSAID prescription in the elderly. Tight glycemic control in the elderly is simply foolish. Cut back on oral hypoglycemic agents in the face of liver or kidney disease.

ANOTHER ONE FOR THE COFFEE-DRINKING CLASS

First, it was found to help against clinical depression, and now comes a Harvard paper by Je et al, *Cancer Epidemiol Biomarkers Prev*, 2011, tracking daily coffee consumption amongst the 67,470 female participants of the Nurses' Health Study. They found that consuming 4 or more cups of coffee (caffeinated or decaf) was associated with a 25% lower risk of endometrial cancer, which was not found in tea drinkers. The researchers hypothesize that the effect of coffee might be through reversal of insulin resistance, and point out that coffee lowers serum levels of insulin and estrogens, both believed to be integral factors in uterine carcinogenesis. The protective effects of coffee appeared to be strongest amongst the obese, post-menopausal and (past and current) smokers. They conclude that 4 cups of coffee a day may protect against endometrial cancer.

POORER OUTCOMES WITH LONGER CLINICAL PRACTICE

Age is rightfully a veritable badge of honor. Whilst older physicians commonly tout their longevity, wisdom and experience, recent data suggests a slightly different picture. Physicians with long years of practice were less likely to follow clinical guidelines and were more likely to have a diminished medical knowledge-base. As if that wasn't enough, Southern et al, *Am J Med*, 2011, studied 6572 hospital admissions by 59 physicians at a New York teaching hospital. Patients of physicians with more than 20 years of practice experience were at higher risk for mortality as well as prolonged in-hospital stay compared to patients of physicians who were 5 years or less out of training. The combination of longer stay (i.e. higher costs) and higher mortality (i.e. worse outcomes) virtually guarantees that someone from CMS is already looking very closely at this study. Which I guess should finally settle that long-running dispute on the need for Board re-certification for "older" physicians.

PREDICTING AMIODARONE-INDUCED PULMONARY SYNDROME

Amiodarone is an effective and commonly used anti-arrhythmic agent. Long-term clinical use is commonly subverted by drug-related adversity such as thyroid dysfunction (both hypothyroidism and hyperthyroidism), skin discoloration, liver and lung toxicity. Amiodarone-induced pulmonary toxicity is insidious in onset, difficult to diagnose (it remains a diagnosis of exclusion in any amiodarone-treated patient presenting with impaired lung diffusion capacity and restrictive defects), potentially serious (with 1-33% mortality), unpredictable, and not uncommon (estimated to occur in 1-8% of long-term users). Jackevicius et al, *Am J Cardiol*, 2011, present a retrospective, population-based cohort study of amiodarone-related pulmonary dysfunction in patients with chronic atrial fibrillation. Amiodarone-related pulmonary dysfunction occurred across the entire dose spectrum, and was associated with advanced age, male gender, history of COPD and underlying renal dysfunction.

CHECK BOTH ARMS: WHY ARM BP DISPARITY MATTERS

A meta-analysis from England, Clark et al, *Lancet*, 2012, confirms that systolic blood pressure disparity between both arms of 15 mmHg or higher should prod further evaluation for underlying peripheral vascular disease. Such differences in systolic BP were associated with peripheral vascular disease (15% sensitivity and 96% specificity) cerebrovascular disease (8% sensitivity and 93% specificity), as well as higher cardiovascular and all-cause mortality. Some studies report that even "trivial" systolic BP disparities of only 10 mmHg were linked to peripheral vascular disease with 32% sensitivity and 91% specificity. In an accompanying editorial, McManus & Mant, *Lancet*, 2011, point out that whilst parallel BP measurements are easier to perform than ankle-brachial indices, the low sensitivity of this maneuver would make it a less than ideal screening tool, but still an "actionable" clinical finding.