Development of Virtual Patients with Neurological Diseases from CT Images of Cadavers

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ABSTRACT:

BACKGROUND: In many medical schools Cadavers form the initial "patient" contact and due to the Health Insurance Portability and Accountability Act (HIPAA), there is very little information available about these "patients" other than the cause of death (COD). Most of the cadavers we dissect are from individuals in their 70s, 80s, and even 90s, therefore it must be assumed that each patient had other medical conditions during their lifetime. Consequently, we decided to develop Virtual Patients (VP) from these cadavers by undertaking CT imagery on many of the bodies prior to their dissection to more fully determine their medical history as radiological analysis offers more information than COD could ever offer.
METHODS: Forty-four bodies were imaged on a CT prior to there being dissected in the gross lab, and from these cases we have developed interactive VP with diseases of the CNS. These VP were created by a team of basic scientists and clinical scientists. Anatomical models were created for each of these cases from the stacks of DICOM collected from our Siemens Somatom Sensation 64 slice, dual energy Computer Tomographic Imaging scanner. The OsiriX and OsiriX -MD program on a Mac Pro computer were used to create anatomical models and videos to illustrate the major findings in each VP.
RESULTS: From these cadavers, we created Virtual Patients by combining the COD and the results of the radiological analysis with the clinical expertise of the development team. Finally using cutting-edge medical imaging technology, we produced interactive VP with self-assessment quizzes and anatomical models demonstrating the anatomical and pathological findings in each case.
CONCLUSIONS: With the aid of a team of basic scientists and clinical scientist and with the cooperation of a Department of Radiology one can develop VP from cadavers which demonstrate the effects of disease in the CNS.

Key Words: Anatomical models, Cadavers, Interactive Cases, OsiriX and OsiriX-MD, Virtual Patients, Videos.

INTRODUCTION

The initial contact with "patients" in many medical schools is with a cadaver [1-6]. Due to the appropriate restrictions of the Health Insurance Portability and Accountability Act of 1996 (www.hhs.gov/ocr/hipaa) [7], the information on each of these bodies is limited to only the cause of death (COD) without any real medical or life history. As most of the cadavers we dissect are from individuals in their 70s, 80s, and even 90s, it must be assumed that each patient had other medical conditions during their lifetime. Therefore, we decided to undertake CT imagery on many of the bodies prior to their dissection to more fully determine their medical history and because radiological analysis offers more information than "cause of death" could ever offer. Virtual Patients are now being used in many settings in the medical, dental and legal profession and they have been shown to be a very important educational tool [8-24]. There are also websites which demonstrate their usefulness [25]. A Virtual Patient is a set of digital information that creates an individual real patient, or a fictional/idealized patient or some combination of the two and includes the results of a medical history and physical examination with appropriate internet cross references. The "virtuality" of these patients is based on there being modeled in data rather than in person.

For our study, we formed a team of Basic Scientists (from Anatomy), and Clinical Scientists (from Neurology and Radiology) to develop Virtual Patients (VP) and anatomical models from the CT images of 44 cadavers we imaged that demonstrated the common cause of death as noted by the CDC [26]From these cadavers, we created Virtual Patients by combining the cause of death (COD) and the results of the radiological analysis with the clinical expertise of the development team and then finally using cutting-edge medical imaging technology we produced anatomical models demonstrating the anatomical and pathological findings in each of these cases. The VPs we developed from these cases were supplemented with interactive self-assessment questions to aid the student in learning the material. The development of these virtual patients extends the value of the Anatomical Gift Program beyond a one-time laboratory dissection, and initiates the interpretation of CT and MRI images to our medical students early in their careers which facilitates the development of clinical reasoning skills. In addition, these VP stimulate our students to study anatomy.

MATERIALS and METHODS

Permission to Image Cadavers. Each body used in this study was from the Tufts University Health Sciences Anatomical Gift Program. These studies have also been approved by the Internal Review Board of Tufts University School of Medicine and follow the guidelines of the Health Insurance Portability and Accountability Act (HIPPA) of 1996. All images are de-identified to prevent the identification of the actual patients.

Embalming Procedure. A total of 44 embalmed bodies were imaged and we labeled them as

Cases "A"- "AR". All the bodies were embalmed within one day of death. Each body was embalmed by infusion through the right common carotid artery with the aid of an Edwards Duotronic Injector Embalming Machine. On the average the pressure was 10 – 15 lbs. and the volume 25-40 liters. These variations are a result of the size of the individual and the proximity to death. Each body was stored in a cold room in a body bag prior to there being placed in the gross lab where they were also stored within the body bag.

Embalming Fluid:

Formaldehyde	4.8%
Phenol	14%
Iso-P-alcohol	55.2%
Propylene Glycol	26 %
Mitrol (for mold)	0.9%

Pilot Study-Cadaver "A". To determine if the images from an embalmed body were useful and of high quality we first obtained CT images of an un-embalmed body, Patient A, within 12 hours of death and after imaging the body was embalmed by infusion.

Cadaver "A". 88-year-old female. The cause of death (COD) was Chronic Obstructive Pulmonary Disease, Pulmonary Hypertension, and Type II Diabetes. The lung appeared normal

Radiological Findings: In the scout image a cardiac pace maker was noted.

After imaging, about 5 hours later Cadaver A was embalmed by infusion of fluids through the right common carotid artery. We then CT imaged the same body two weeks after embalming, and the radiologist, Dr. Polak, compared the images before and after embalming and noted that the DICOM images in most regions were of high quality and similar to those obtained shortly after death and without embalming. This pilot study also showed us that we could use embalmed bodies to demonstrate the anatomical features, and that we could obtain excellent images from embalmed cadavers even several months after they were prepared thus permitting us flexibility in undertaking the imaging.

CT Imaging Protocols. For this study a total of 44 embalmed bodies were imaged on a Siemens Somatom Sensation 64 slice dual energy Computer Tomographic Imaging scanner in the Department of Radiology at the Tufts Medical Center. Each body was placed in a body bag and then imaged in the CT. The preliminary results from 12 cadavers were presented in a short publication in 2009 [3]). Another 32 cadavers were imaged with the study now including 25 females (average age of 82+/-10 years) and 19 males (average age of 75 +/- 7 years).

The system was setup to image the length of the torso, abdomen and lower extremities in one scan (resulting in 700-1200 images) and the head and neck in a separate scan (resulting in 150-250 images). One mm slices were collected, 512x512 in-plane image (¾ mm spatial resolution). Image reformat was performed in the coronal plane using a 3mm X 3mm pixel size. Main detector energy was set at 120 KV and the Field-of-View at 380 mm. Rotation of the gantry was set at 0.5 seconds and collimation at 2 mm slice thickness in the axial plane on the scanner workstation (Leonardo). Image reformatting was performed in the coronal plane using a 3mm X 3mm pixel size. Images were stored in three image sets: standard soft tissue, lung and bone windows. A complete set of CT images at high resolution were obtained.

Visualization of Arteries. To better demonstrate the arterial system in the reconstructions, in several cases we initially added gadolinium contrast media to the embalming fluid and we were not successful with these compounds. With further experimentation, we found that by simply pumping air into the arterial system for ten minutes after the conclusion of the fluid infusion we could demonstrate the arterial system (Figure One). Therefore, in cases "N"- "AR" after the embalming fluid was run through the body, the embalming machine was run for another 5 minutes resulting in air being pumped throughout the arterial system with the vascular system identifiable by the zero-density air. The CT scans of cadavers with air permitted us to better viewing the vascular tree and is nearly as useful as scans of living beings with contrast added into the vascular system.

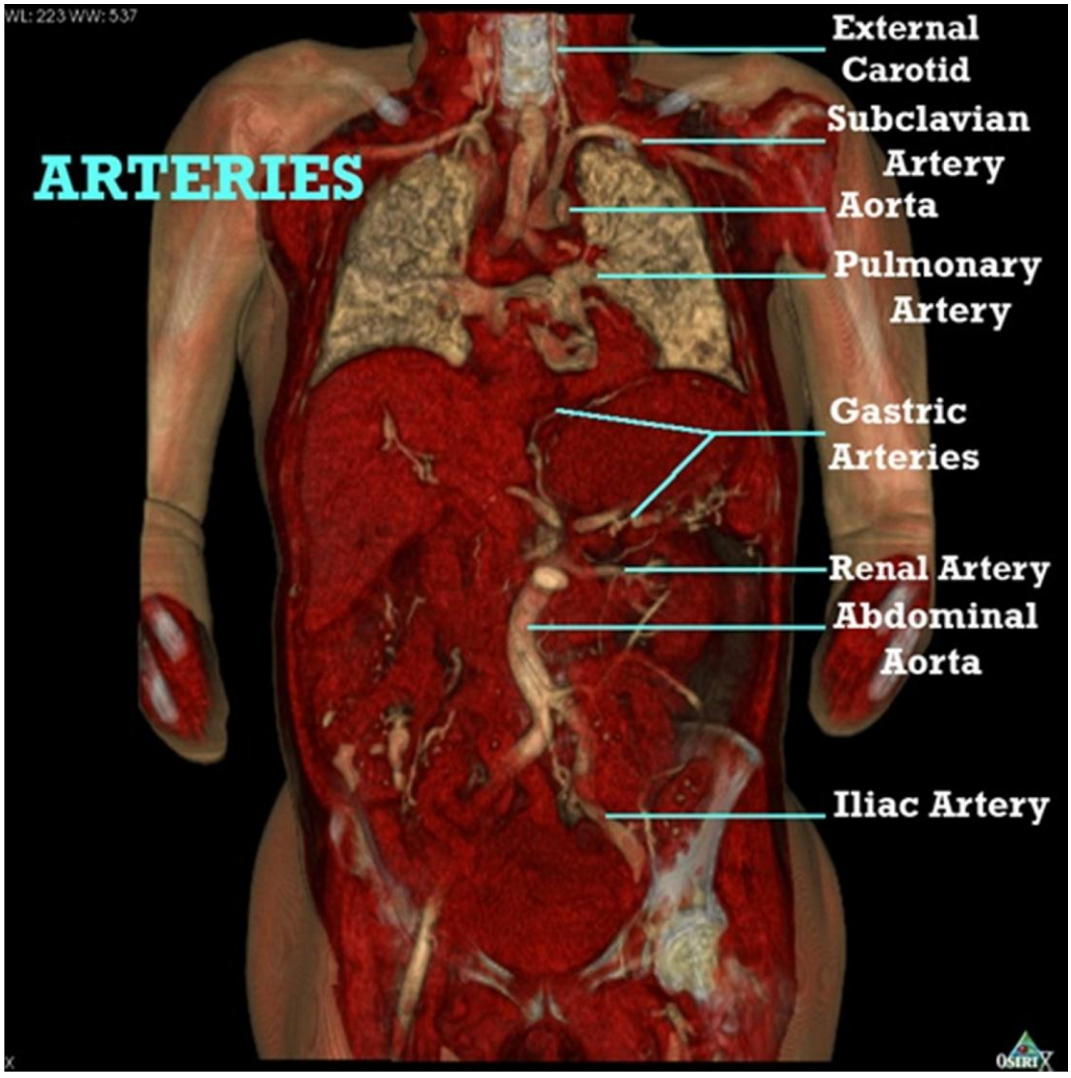

Figure One, Case W. Demonstration of major arteries after infusion of air via common carotid. OsiriX- 6.

Creation of Anatomical Models-Image Analysis/Volume Analysis -OsiriX Program on a Mac Pro. The OsiriX programs [26] were used throughout this study to construct the anatomical images from the stacks of DICOM images which were then labeled using Adobe Photoshop to fully illustrate the anatomical and pathological findings which formed a virtual patient. We have used two versions of OsiriX, the 32-bit Open Source version or the 64-bit OsiriX MD (both available from Pixmeo in Switzerland) for the MAC [26]) program on an Apple Macintosh Desk Pro or a MacBook Pro. We found the 64-bit OsiriX MD 7.0.1 program better for developing 3D anatomical models. OsiriX or OsiriX MD program identifies a cluster of points with similar densities, surrounded by a shell of much higher density, so it reconstructs this into a three-dimensional representation for all organs. OsiriX also allows the user to assign colors to different densities, so anything with the density of bone can be designated to be for example cream colored, whereas anything

the same density as liver can be colored maroon. We saved each color scheme as a profile, so that we could easily assign appropriate colors to view different systems: muscles, bones, brain, vascular, pulmonary etc.

Creation of Virtual Patients with disease of the CNS. In all of the cases due to the HIPPA laws we have very little personal information other than their age, sex, and cause of death. Therefore, we created Virtual patients, a digital patient, created from a combination of the findings in the radiological images and the clinical expertise of the internist from actual patient data

We created a virtual patient for each patient by the amalgamation of the radiological findings, COD, and the clinical expertise of the case history developers. Space limitations in this journal does not allow us to present each of the 44 Virtual Patients with their images, consequently we have focused this study on cases that represent a broad spectrum of neurological diseases in the body and fully illustrate the educational value of imaging cadavers prior to their dissection. The following cases in bold-Table one. illustrate some of the common causes of disease of the CNS -1) Cerebrovascular Stroke-Case AF; 2) Neurodegenerative diseases, Case D-Alzheimer's' Disease, Case M-Parkinson Disease; Case Q-Amyotrophic Lateral Sclerosis (ALS); 3) Metastatic Lesion to the brain from the lung of a patient who was a heavy smoker-Case K; 4) Traumatic brain injury (TBI): Case AS-Subdural from a fall in a nursing home. For each case, we have included Self-Assessment questions (Q) with their answers (A).

Creation of Videos. From the cases discussed in this paper, videos were created from the stack of DICOM images using QuickTime Pro and we have placed a video from Case Y on ITunes/Tufts and braindementia.net. Each video includes a running commentary and an anatomical model with labelled JPEGS and TIFFS inserted to illustrate major anatomical and pathological findings. The final version can be viewed with any digital-viewing software. We are currently creating more videos of Virtual Patients in the QuickTime Pro format from our cadavers and we are in the process of storing them on the braindementia.net for easy access to students or other interested parties.

.TABLE ONE. List of bodies CT Imaged, with the Case ID, age and sex of patient include and finally the Cause of Death listed. The cases discussed in this study are marked in BOLD.

TABLE ONE. List of Bodies CT Imaged

CASE	AGE and Sex	CAUSE OF DEATH & OTHER OBSERVATIONS
A "Pilot"	F 88	COPD, Pulmonary Hypertension. Type II Diabetes; First imaged un-embalmed and then after embalming re-imaged 2 weeks later**.**
B	F 91	Myeloplastic anemia, Rheumatoid arthritis
C	M 81	Intracerebral Hemorrhage
D	**F 86**	**Alzheimer's dementia**
E	M 67	COD Stage IV colon cancer
F	F 37	Aggressive Breast Cancer, Hepatic failure
G	M 74	Myocardial infarction and heart rupture (tamponade)

H	M 77	Emphysema, smoking
I	F 82	GI Bleed, Coronary artery disease, Peripheral vascular disease, COPD
J	F 84	Intracerebral hemorrhage
K	**F 83**	**Metastatic lesion into brain from primary in lung**
L	M 89	Hodgkin's' Lymphoma, Arteriosclerotic heart disease, Hip replacement
M	**M 77**	**Subdural hematoma, Alzheimer's, Parkinson Disease**
N	M 52	Ischemic Bowel disease, Metastatic esophageal cancer
O	M 67	Stage IV Colon cancer
P	F 86	Alzheimer's dementia with shunt
Q	**M 61**	**Respiratory arrest, Pneumonia, ALS**
R	F 76	Alzheimer's, hip replacement
S	F 96	Cardiac arrest, Asystole, Electrolyte abnormalities, Acute renal failure, Guillain-Barre syndrome, Congestive heart failure, Atrial fibrillation, Neck fracture
T	F 66	Metastatic breast cancer
U	M 97	Respiratory failure, Pleural effusions, Pneumonia, Asbestosis
V	F 63	Cardiogenic shock, MI infarction, Diabetes, Hypertension
W	M 66	Failure to thrive, ALS
X	M 81	ischemia, cerebrovascular accident, atrial fibrillation
Y	F 81	Ovarian Cancer
Z	M 63	Pulmonary emboli, Pancreatic cancer
AA	M 82	Intracranial hemorrhage from glioblastoma, knee replacement
AB	F 91	Cardiopulmonary, arrest, dementia, subdural/epidural
AC	F 98	Advanced Age, heart failure, thin, AAA
AD	M 76	Pancreatic Cancer
AE	M 89	Pick's Disease
AF	**F 91**	**Stroke**
AG	M 68	Metastatic Colon Cancer, Hip Replacement
AH	M 85	Non-traumatic intracranial hemorrhage, hypertension
AI	F 85	Sudden cardiac death, coronary artery disease
AJ	F 89	Chronic kidney disease, Alzheimer's, dementia
AK	F 86	Colon Cancer
AL	F 98	Respiratory failure, congestive heart failure
AM	F 94	Peripheral vascular disease
AN	M 85	AAA pneumonia, aspiration, dysphagia, Cerebrovascular accident

AO	F 98	Hip repair, Inanition, dementia, cardiovascular disease
AP	F 68	Lung Cancer
AQ	F 93	Alzheimer's disease
AR	F 43	Metastatic Breast Cancer

RESULTS

Abnormal and Pathological Findings/Patient.

From each cadaver, the CT images were reviewed by the radiologist, Dr. Polak, and all the major normal and pathological findings were listed on each section. In all the bodies, we imaged the radiologist noted an average of six abnormal and pathological findings per imaged cadaver (range, four to 12 findings). Many of the major findings were directly associated with the reported cause of death (e.g. large right cerebral hemispheric infarction in a patient with a reported a cause of death of left-sided stroke, several AAA, and many cases of Alzheimer's disease, and an ovarian tumor). However, the majority of the pathological findings were unexpected including knee replacement, hip replacement, hip repair, pleural and pericardial effusions, ascites, metastatic lesions, arterial grafts, enlarged prostate, enlarged thyroid gland (goiter). In addition, there were many unreported surgical procedures including cholecystectomy, hysterectomy, splenectomy, and vascular shunts. These pathological conditions and surgical procedures were revealed because of the analysis of the images by the radiologist.

In this study, we selected representative cases from the 44 bodies we preimaged (Table One) which illustrate diseases in the CNS, and we have focused on developing VP with major Neurological Syndromes as we plan to use these VP in our Neuroscience course. We have added Case AS, which illustrates the effects of trauma to the brain.

The preliminary results from 12 cadavers were presented in a short publication in 2009 [Jacobson et. al 3] and was finished over the last three years with 32 more cadavers were imaged with the final study having 25 females (Table 1; average age of 82+/_10 years) and 19 males (average age of 75 +/- 7 years) [4]. They were all im- aged inside a body bag on the Siemens CT in the Department of Radiology at the Tufts University Hospital in Boston prior to there being dissected in the Gross Lab of Tufts University School of Medicine.

Virtual Patients with Disease of the Central Nervous System.

1) **CEREBROVASCULAR DISEASE**.

CASE AF, Figure 2. Mrs. AF is an 91-year-old right handed female with no-table pmhx including 50 pack/year smoking history, HTN, HLD, type 2 diabetes, divertic-ulosis and BPH who presents to the emergen-cy department with a chief complaint of left upper extremity weakness, numbness and "stuttering speech". As a neurology resident, a stroke alert is paged out to your beeper prompting your assessment. Upon initial evaluation of the patient, you note the patient's blood pressure to be 182/94 however note otherwise normal/stable vitals. The patient is alert and oriented and you receive sign-out via the EMS team. You take a second and glance at the patient's chart.

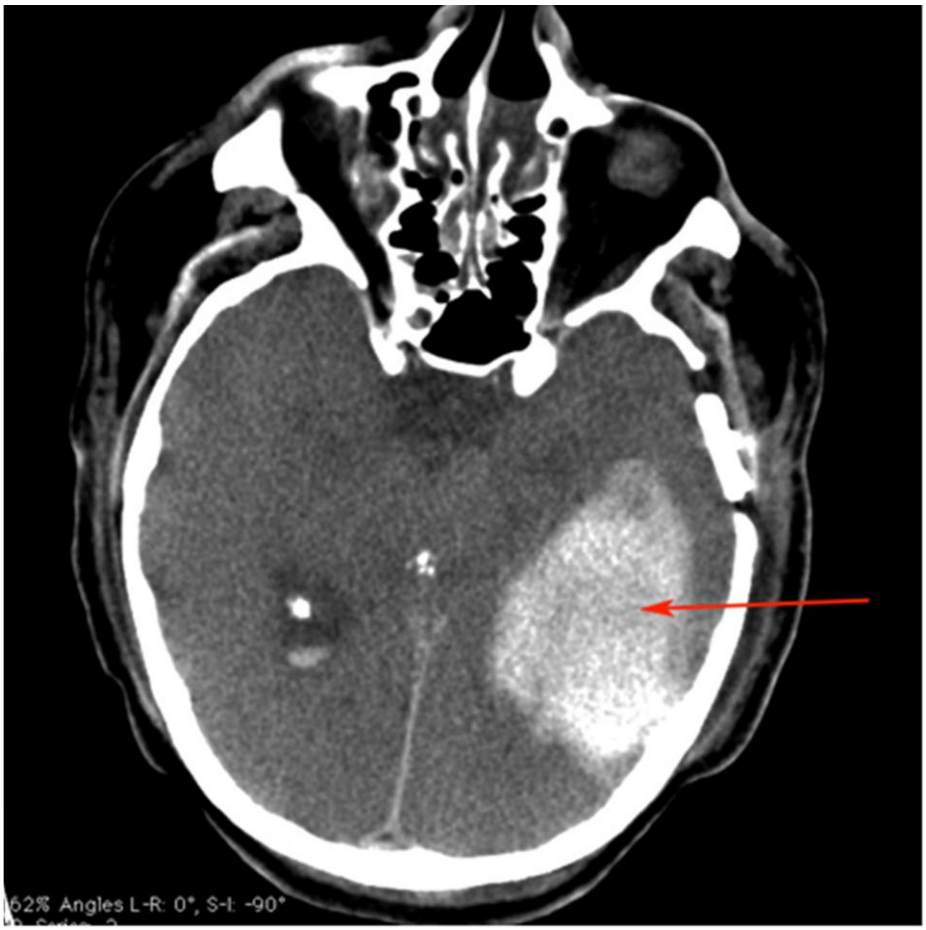

Fig 2. Case AF. 91 y.o, female with Intracerebral Hemorrhage (arrow) in right MCA affecting frontal and parietal lobe producing the stroke. CT.

Q1.) What are the patient's risk factors for stroke?

A1.) General stroke risk factors include: Hypertension, hyperlipidemia, tobacco use, heart arrhythmia (in particular, atrial fibrillation) type 2 diabetes mellitus.

Q2.) What is the most important information regarding the timing of the patient's symptoms?

A2.) Last time normal (LTN). LTN is essential in the initial evaluation of a potential stroke case. The clinical incidence falls within the context of tPA (tissue plasminogen activator) and potential for neurological endovascular intervention. The clinical trials of NINDS and ECASS III suggest intervention within 3-4.5 hours provides greatest benefit therefore, it is incredibly important to clarify the LTN. Per EMS report, the patient's time of onset is unclear. He reportedly awoke that morning at approximately 8am with the present symptoms. EMS was called shortly thereafter and upon arrival to the ED at 8:32am, stroke alert was called. At this time, you move to the patient's bedside and introduce yourself.

Q3.) What is the next step in your evaluation of the patient?

A3.) As described above, clarification of the patient LTN is essential. In this patient, he reports awakening with the symptoms. However, unable to clarify the patient's LTN before imaging (using the rest room, awakening

for a phone call etc.) you move to perform a NIHSS.

Q4.) What is the NIH stroke scale? How can this be used in the initial assessment of the patient?

A4.) The NIH stroke scale is a standardized assessment tool used in evaluation all varieties of stroke patients which consists of 11 different criteria including level of consciousness observed, questions and commands, gaze assessment, visual assessment, facial palsy, motor assessment in all four extremities, limb ataxia, sensory, best language, dysarthria, extinction. The usefulness of this tool is that it is a concise and standardized assessment focusing on a compilation of symptoms that may be found in a compilation of different stroke etiologies. Based on a standardized score, criteria for IV tPA include NIH >4, and for endovascular intervention >6. Upon assessing the patient, your exam reveals a NIH of 7 including severe dysarthria, partial left facial palsy, partial extinction in the left upper extremity and sensory changes.

Q5.) What is the next best step in assessing this patient?

A5.) Non-contrast head CT is the principle step is assessing patient's presenting with suspected stroke. On head CT, an intracranial bleed is noted which is an absolute contraindication for IV tPA. This is only one of the many absolute and relative contraindications for tPA which include multiple components of history, current medications and lab/vitals. Additionally, with NIH>6 suggesting a large vessel infarct.

Q6.) Where would you expect to find to localize the stroke and clot (if present).

A6.) With symptoms of dysarthria, left upper extremity weakness and numbness and extinction, this suggest an infarct within the cortex of the frontoparietal territory of the right middle cerebral artery (MCA). Dysarthria is a component of a patient's speech while aphasia is a component of a patient's language. In >95% of left handed individuals, a patient's language center is located in the left cerebral lobe (frontal and temporal). This patient is presenting with dysarthria which can be seen in both right and left cerebral infarcts and therefore does not localize the lesion to the left in this patient's case.

Q8.) What should you order upon admitting the patient?

A8.) The patient has suffered a large vessel, right MCA territory infarct. Given the MCA blood supply is of the anterior circulation, this is likely secondary to atherothrombotic disease; further supported by the patient's history of hyperlipidemia, hypertension, diabetes and tobacco use. CT (Fig 2) reveals a large right fronto-parietal infarct with restricted diffusion on DWI. A SBAR analysis is performed (Situation, Background, Assessment, and Recommendation) which shows a <50% stenosis of the right internal carotid artery, and no signif-icant stenosis within the left internal carotid artery. The patient is subsequently found to have a proximal right MCA thrombus. At this time, you order a hyper-acute MRI and reach out to endovascular neurology who review the imaging. Following their evaluation, the clot is noted to be too distal for endovascular intervention. You notice on routine telemetry evaluation that the patient appears to be in irregular-irregular rate and rhythm. You perform an EKG which confirms your suspicion of atrial fibrillation. The patient should additionally be evaluated by supplemental therapy services depending on their symptomology including speech, occupational and physical therapy. Recommendations provided by these services can be very helpful in assessing for the need of feeding tubes, home health services or inpatient rehabilitation. Basic lab evaluation should include CBC, CMP, a1c and lipid panel (with LDL goal <100 in stroke patients without diabetes; LDL goal of <70 in patients with diabetes). DVT prophylaxis should be given to all stroke patients in the form of sequential compression devices and/or LOVENOX/subcutaneous heparin. For

non-tPA patients, blood pressure guidelines include allowing permissive hypertension up to 220/120 in the first 24-48hrs.

Q9.) What is the next best step in assessing for treatment of this patient?

A9.) Patients with a history of atrial fibrillation should be evaluated by the CHADS2-vasc score. This score is used to assess for the risk of stroke in patients with atrial fibrillation by considering a patient's age, sex, and history of risk factors including hypertension, heart failure, prior stroke/TIA, vascular disease and diabetes. This patient's score is 4 suggesting a 4.8% risk of stroke annually. Patients with a score of 1 or greater should be considered for antiplatelet (aspirin) or anticoagulation. Patients with a score of 2 or greater are recommended to receive anticoagulation. Warfarin is the typically first line agent however depending on other circumstances, novel agents may be considered. In patient with hemorrhagic stroke it is important to control the BP and stopping any medications that could increase bleeding (e.g.- Warfarin or aspirin). This patient was stabilized and successfully transferred to a rehab facility, but expired shortly after transfer to the rehab center.

Comment: Stroke is the fifth most common cause of death in the US resulting in 130,000 deaths (CDC 2016). This patient with their atrial fibrillation, heavy smoking, diabetes and hypertension is at risk for this stroke which produced a hemorrhage into the parietal lobe. If this condition had been due to a blood clot, this patient could have been added by a surgical removal of the clot and treatment with coumadin. The National Institute of Neurological Disease and Stroke of the National Institutes of Health is dedicated to the eradication and treatment of stroke in the USA and the world. (www.ninds.nih)

2) NEURODEGENERATIVE DISEASES.

Figure 3. Gross Brain from Case D, 86 y.o. female with Alzheimer's' Disease, showing wide-spread neuronal atrophy as demonstrated by wide sulci throughout the cerebral hemisphere.

a) **Alzheimer's Disease-CASE D, Figure 3.** Mrs. D is a 86 y/o female with a notable past medical history of moderately controlled HTN and HLD who presents to her primary care physicians office with a cc of chest pain and shortness of breath for an approximate 4-week duration. She is accompanied by her daughter who notes some concern in regards to her mother's memory and accompanying confusion. When questioned about her symptoms, the patient describes her chest pain and shortness of breath as intermittent and occurring simultaneously. She notes the pain as occurring spontaneously which is described as sharp, intense and on average is an 8/10. She denies any focality, migration or positional quality, and states the pain comes on quickly typically; often presenting upon awakening in morning. Neither the pain nor shortness of breath is present at baseline and the only relieving factor identifiable has been deep breathing techniques.

ROS. The patient denies any recent vision changes, pre-syncope, headache, dysphagia or GI symptoms. Her daughter does report some weight loss (approximately 10 lbs. over the last month) and anorexia which she believes surrounds these episodes of pain. Additionally, the daughter notes a decline in cognitive function that has become more noticeably apparent over the past month. She describes her mother as more forgetful; often leading to her becoming confused and occasionally even agitated (as seen in a previous episode where her mother forgot where she was)

Q1): what is your differential diagnosis in this patient. A1): this patient's differential includes Anxiety, pseudo-dementia, Alzheimer's, vascular dementia, hypothyroidism, Korsakoffs/wernickes-Korsakoffs, hepatic encephalopathy, TIA normal age related changes.

Q2): what would be your work up for this patient? A2): vitals, CBC, CMP, Albumin, TSH/T4. The Mini Mental State Exam is widely used and it records; short- and long term memory, attention span, concentration, language and communication, ability to plan and understand instructions.

Q3.) What are the different types of dementia? Which ones are most prevalent?

A3.) Alzheimer's, vascular, mixed, Lewy body, Parkinson's, fronto-temporal/Pick's, CJD, NPH, Huntington's.

Q4.) What are some of the more common side effects of dementia?

A4.) Anxiety, major memory disorders, inability to plan or follow instructions.

Q5): what radiological findings would you expect to see in this patient.

A5): while there are no findings on CT that specifically identify depression or anxiety attacks, global neuro-atrophy is a common pathology seen in patients with late stage dementia/Alzheimer's. 6.) What options do we have to treat Mrs. Gardner?

A6.) Mrs. D is prescribed a selective serotonin reuptake inhibitor(SSRI), and though initially is hesitant to take it, soon notices a decrease in her anxiety attacks. Her daughter reports better sleep, appetite and overall quality of life. The patient additionally is trialed on a course of Aricept; an acetylcholinesterase inhibitor. She dies of pneumonia several months after you see her.

Comment: In our aging population, there are about 5,000,000 cases of Alzheimer's disease which is usually progressive, and puts extreme burdens on a family's social structure and finances. There is no successful treatment yet to reverse or reduce the effects of this disease which affect the patient and their family. There are many strategies available to keep one's mentation in the normal effects of aging including mental and physical activities.

There has been much work on pharmacological agents to reduce the amount of amyloid-B and tau protein which accumulates as the neurons die and may produce many of the problems in mentation seen in this disease. The NIH and the Alzheimer Organization is very active in trying to alleviate the effects of this disease on the patient and family and active in trying to find a cure (www.alz.org.).

b) **Parkinsons' Disease, CASE M (Figure 4).** Mr. M is a 77-year-old male who presents to your office with a chief complaint hand tremor. The patient reports that beginning approximately 4 months ago, he began to develop a tremor in both of his hands. He denies the tremor as bothersome however his son (who accompanies him today at the appointment) notes that the tremor has become worse over the past month and that it can potentially get so bad that the patient will knock over nearby objects with his elbows without knowing. Upon reviewing the patient's chart, you see that he has a past medical history notable for hypertension, bipolar disorder, chronic back pain, and multiple concussions during his career as a minor-league hockey player. Upon review of systems, the patient describes feeling at his normal baseline, without any recent fevers, chills, shortness of birth (SOB), chest pain, gastrointestinal (GI) or genitourinary (GU) symptoms

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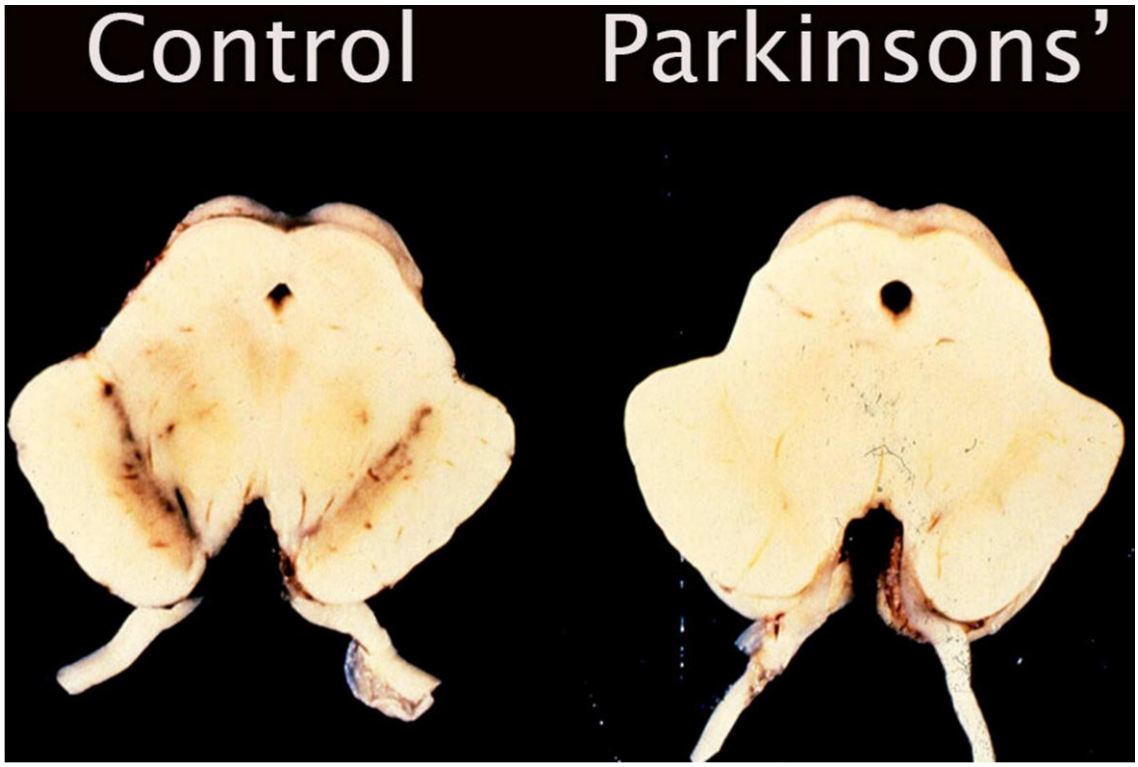

Figure 4. Gross Midbrain. On left the substantia nigra of a normal/control patient with melanin pigmentation, and on the right the substantia nigra of Case M, a 77 y.o. patient with Parkinsons' Disease (PD), demonstrating depigmentation in the pars compacta of the substantia nigra due to apopotosis/cell death with resultant reduced activity of dopamine se-creting cells producing the PD.

Q1: What would you like to know next about the patient's tremor? A1: The main distinguishing characteristics regarding essential tremor and one involving a more complex diagnosis such as Parkinson's is whether the tremor occurs at rest or during specific tasks. When questioning the patient, he and his son report the tremor occurs at rest; particularly while watching TV. Typically, the patient doesn't appear to have difficulty when performing tasks such as buttoning his shirt, turning a door handle or writing, though he notes his father's penmanship has become quite small and difficulty to read; particularly decreasing in size as he writes.

Q2: What additional information might you want to ask the patient? A2: When thinking about diseases that may cause resting tremor, with the patient's demographics it would be important to ask about any changes in gait, balance, additional abnormal movements, difficulty with reading, writing or memory, and any language or speech changes. When asked, the patient's son does note some recent changes in the patient's gait in which he describes the patient as almost "stuttering his feet" at the initiation of walking as well as very low, wide turns that time him seem unnecessarily long.

ROS. You proceed with the physical examination which reveals a healthy appearing male with evidence of resting tremor. Cranial nerve evaluation is unremarkable for focal deficits however apparently reveals decreased facial expression (which is further supported by the patient's son). Strength and sensation are intact and grossly normal in all four extremities and reflexes +2 throughout upper and lower limbs. Upon circumferential rotation of the elbow and wrist, cogwheel rigidity is noted bilaterally. Upon asking him to extend for finger-to-nose exam, the patient can do so without dysmetria. Rapid alternating movements however reveal delayed and slow response and kinesia. Gait reveals a wide base with a shuffling pattern during initiation. The patient takes multiple steps when turning 180 degrees. When asked to close his eyes and slightly pushed to one side, the patient notably has a difficult and delayed reaction time with inability to fully catch himself from falling. You further review the patient's current medications and ask if there have been any recent changes, in which the patient states there was a change to one of their psychiatric medications.

Q3: What would you be most interested in learning regarding this change in the setting of this patient's current symptoms? A3: The patient currently is currently displaying symptoms consistent with Parkinson's disease. Due to PDs physiology of decreased dopamine availability, it is important to differentiate whether this is truly secondary to PD or whether medication induced. Medications that may result in a Parkinsonism state are typically agents used to treat schizophrenia or manic episodes in bipolar disorder as these diseases are a result of excess dopamine; therefore, antipsychotic agents block the release of this agent. If given too high of a dose of these medications, a patient may experience too far of a shift in the opposite direction; thus, displaying a Parkinsonism presentation. The patient's son can recall the recent change to the patient's medication and notes a decrease in the patient's blood pressure medication and notes that the patient has never required treatment with an antipsychotic. You additionally review recent lab work performed by the patient's PCP in which lipids, TSH, A1c and BMP all return within normal limits.

Q4: You are now concerned that the patient may have PD. Does this patient meet the criteria for diagnosis of Parkinson's disease? What additional historical information points you towards or away from this diagnosis? A:4 Yes, the patient meets the diagnostic criteria

by the following: Bradykinesia in addition to at least one of the following: muscular rigidity, resting tremor, postural instability. Mr. P meets the all four criteria with bradykinesia seen on rapid alternating movements, resting tremor, cogwheel rigidity and shuffling gait with balance difficulty. The patient additionally presents with micrognathia as well as most concussions during his career as a hockey player. The patient also reveals masked facies (noted with decreased facial expressions).

Q5: What additionally helps support the diagnosis from a pharmaceutical standpoint? A5: Given that Parkinson's is a disease of decreased dopamine production, such patients should in theory respond well to supplementation. Using medications such as (cavidopa/levodopa) which both provides additionally dopamine while preventing the peripheral metabolism of the compound, the diagnosis of Parkinson's can be supported by evaluating the patient's response. By giving high dose therapy (>1000kg a day) patients who do not show response to the medication are very unlikely to have Parkinson's and an alternative diagnosis should be investigated.

The patient additionally presents with micrognathia as well as most concussions during his career as a hockey player. The patient also reveals masked facies (noted with decreased facial expressions). Q6: Is there any other test available to help diagnosis our patient? A6: Parkinson's patients can receive DaTscan which allow physicians to use a radionucleotide to assess for how much dopamine is available in a patient's brain. The scan is NOT used to diagnosis Parkinson's but rather support the diagnosis and argue against other diagnoses such as essential tremor which do not result in decreased dopamine availability. That said, it is important to note that there are additional diseases such as multiple system atrophy or progressive supranuclear palsy which can also produce a loss of dopamine in the brain and therefore, DaTscan cannot be used to differentiate between these diseases.

Comments: There is currently no known treatment that will reverse the neuronal degeneration seen in PD with 200,000 cases noted annually, and it is the second most common form of neurodegenerative disease after AD. Given that Parkinson's is a disease of decreased dopamine production, such patients should in theory respond well to supplementation. Using medications such as (cavidopa/levodopa) which both provides additionally dopamine while preventing the peripheral metabolism of the compound, the diagnosis of Parkinson's can be supported by evaluating the patient's response. In cases where patients do not respond to the medical treatment, electrodes can be stereotaxically inserted into the subthalamic nucleus in the diencephalon where high frequency deep brain stimulation may relieve the tremor. The Parkinson organization is dedicated to the control and eradication of PD (www.Parkinson.org.)

c) **Amyotrophic Lateral Sclerosis-Case Q, Figure 5 and 6.** Mr. Q is a 61 y/o 26 pack/year smoker male with notable past medical history including GERD (gastroesophageal acid reflux), HTN (hypertension) and HLD (hypertensive lung disease) who presents to your office for a follow up physical. Mr. Q is well known to you due to his multiple attempts at tobacco cessation over the past ten years. Upon reviewing Mr. Q 's chart prior to entering the exam room, you see that the patient was most recently seen 9 months ago, at that time, he appeared to be at his baseline help aside from some tingling in his right big toe. With a BMI-body mass index of 32, family history of type 2 diabetes and HgA1c of 6.3 (hemoglobin A1c above 5.6 abnormal.), you recommended diet and lifestyle modification and warned that

this tingling may be the early features of peripheral neuropathy. You are surprised to see that Mr. Q has requested an appointment so soon, and you enter the exam room. Upon greeting Mr. Q., you note that he has a walking cane, and you ask what has brought him in to see you today? The patient begins to explain that his right big toe won't stop twitching and it's driving him "crazy". He reports the twitching started shortly after last seeing you 9 months ago, and has been increased in frequency and severity of the twitching. The patient describes the twitch as initially occasional and would only occur after long days on his feet and lying down in bed. He notes being able to control the twitching when he noticed it by actively dorsiflexing his first right toe or plantar-flexing his right toes. However, he notes that over the past two months, he has been unable to resist and contain the twitching and that he may even just be sitting in a chair and his toe will be twitching uncontrollably.

Figure 5. The gross muscle atro-phy seen in patient Q with ALS upon postmortem examination.

Figure 6 is a section from the spinal cord of a patient with ALS showing bilateral demyelination in the corticospinal tract due to upper motor neuronal atrophy.

Figure 5. Neurodegeneration. ALS. Case Q, Scout CT image demonstrating the atrophy in the limbs of this 61-y-o. patient with ALS. Osirix 6.

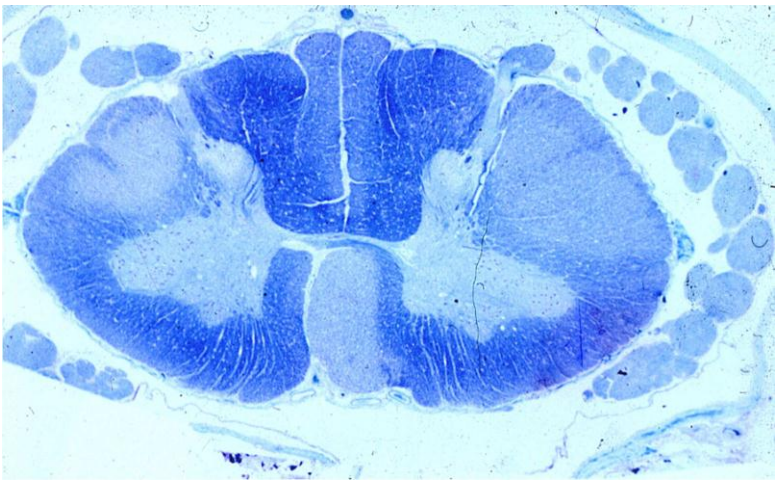

Figure 6. Neurodegeneration. Histological section at Cervical spinal cord level from a patient with ALS demonstrating demyelination bilaterally in the corticospinal tract and atrophy of the ventral horn cells. (Luxol-Fast Blue)

Q1: What would you like to next ask Mr. Q?

A1: You would like to know if Mr. Q. has been experiencing any other new or accompanied symptoms. Is this twitching associated with pain or parathesias? Is it only located in his right big toe or does it migrate? Mr. Q. notes that aside from his right big toe, he recently has developed twitching/shaking of his left hand, and weakness in his right leg. He denies the twitching throughout as painful however it can be associated with parathesias. He notes these symptoms initially waxed and waned, but recently they have been persistent and without relief. The weakness in his right leg has become so significant that he now always needs a cane.

Q2: What other information about the patient's past history might be helpful in your evaluation of Mr. Q.

A1: Any recent trauma. Family history (diabetes, MS, muscular dystrophy, ALS, CIDP, malingering?) PMH (stroke? Has HTN, HLD, DMT2(adult onset diabetes) smoker).

ROS (review of systems): Denies any LOC, dizziness, vision changes, chest pain, dysphagia, dysarthria, GI symptoms, urinary symptoms or new rash. Notes the weakness and tingling as described above. Additionally, notes some SOB over the past few weeks.

Vitals: T: 98.7, P: 85, RR: 32, BP: 132/88, SaO2: 93%

PHYSICAL EXAM:

General: AOx3, in mild distress

HEENT: atraumatic and normocephalic, EOMI (extra ocular movements) and PERRL (pupils equal, round react to light), no nystagmus, neck is supple and w/o LAD (, MMM

Cardiac: RRR, normal s1/s2, w/o evidence of murmur

Respiratory: Notably use of assessory muscles to help in breathing, lung fields clear to auscultation b/l, no evidence of wheezing, rhonchi or crackles.

Abdomen: non-tender throughout, normal bowel sounds, non-distended, no HSM or mass appreciated.

Neuro: CNII-XII intact and w/o focal deficit.

MOTOR: no pronator drift noted. 4-/5 in right wrist flexors and interosseous Abductors.; left side 5/5 respectively. 5/5 in deltoid, biceps, triceps b/l. Left hip flexion 3-/5; right hip flexion 5/5. Hip extension, knee flexion +extension, ankle flexion flexion 5/5 b/l.

DTR: 2+ and symmetric in biceps, triceps b/l; 3+ in left patellar, 2+ in right patellar. Plantar

reflexes are flexor.
SENSORY: light touch, pinprick, position sense and vibration sense are intact in fingers and toes.
COORDINATION: rapid alternating movements are intact; fine finger movements on left are intact, however restricted on the right; some dysmetria appreciated on finger-to-nose b/l; unable to perform heel-knee-shin or Romberg due to inability to stand without cane. GAIT: reduced with need of cane; unable to assess free arm swing.

Q3: What is your differential now? What labs would you like to order?

A3: ALS, MS, CIDP, electrolyte disturbance, diabetes, trauma. CBC, BMP, HgA1c., SPEP + UPEP, TSH, heavy metal urine tox screen.

Q4: What else would like to order?

A4: EMG + NCV, brain MRI, myelogram of cervical spine.

Q5: What additionally can you offer?

A5: nerve + muscle biopsy.

Comment: ALS is a disease of both upper and lower motor neurons. (Figure 5 is a postmortem scout images of Case Q showing wasting of the limb muscles). Figure 6 is from another case of ALS demonstrating atrophy of the corticospinal tract (upper motor neuronal dis-ease and atrophy of the ventral horn cells-lower motor neuron disease). In many cases the individuals has had significant trauma to the head and neck. There is currently no reg-imen that stops the progression of this insidi-ous disease which is usually fatal within 1-3 years after onset. The ALS society of the US is supportive of those with this disease and working to eradicate this disease (www.als.org).

3.METASTATIC LESION IN THE BRAIN. Metastatic/Tumor from lung onto brain, CASE K, Figure 7A and 7B.

Mrs. K. is a 83 y/o female who presents to your office with a chief complaint of shortness of breath (SOB). The patient has requested an appointment for "really bad chest issues. Upon reviewing her chart, you find that she has a past medical his-tory including a 40 pack/year history of tobacco abuse, hypertension, hyperlipidemia and remote history of alcohol abuse. Upon greeting the patient, she explains that she has been experiencing significant shortness of breath beginning approximately 2 months ago. She reports that initially her symptoms were limited to exertion; particularly when walking up a flight of stair. However, the patient now reports that she has been experiencing persistent shortness of breath, chest heaviness and productive cough present for the last three weeks. When asked to described her symptoms, she states the heaviness is generally on the right side however seems to involve her entire chest. She reports worsening of the discomfort when taking deep breathes however additionally states the sensation can occasionally cause a pain. Regarding her productive cough, the patient reports a thick dark yellow/green sputum for approximately three weeks which has recently become more of a brown color with small red specks in it. The patient otherwise denies any contributory family history, and continues to smoke daily two packs of cigarettes.

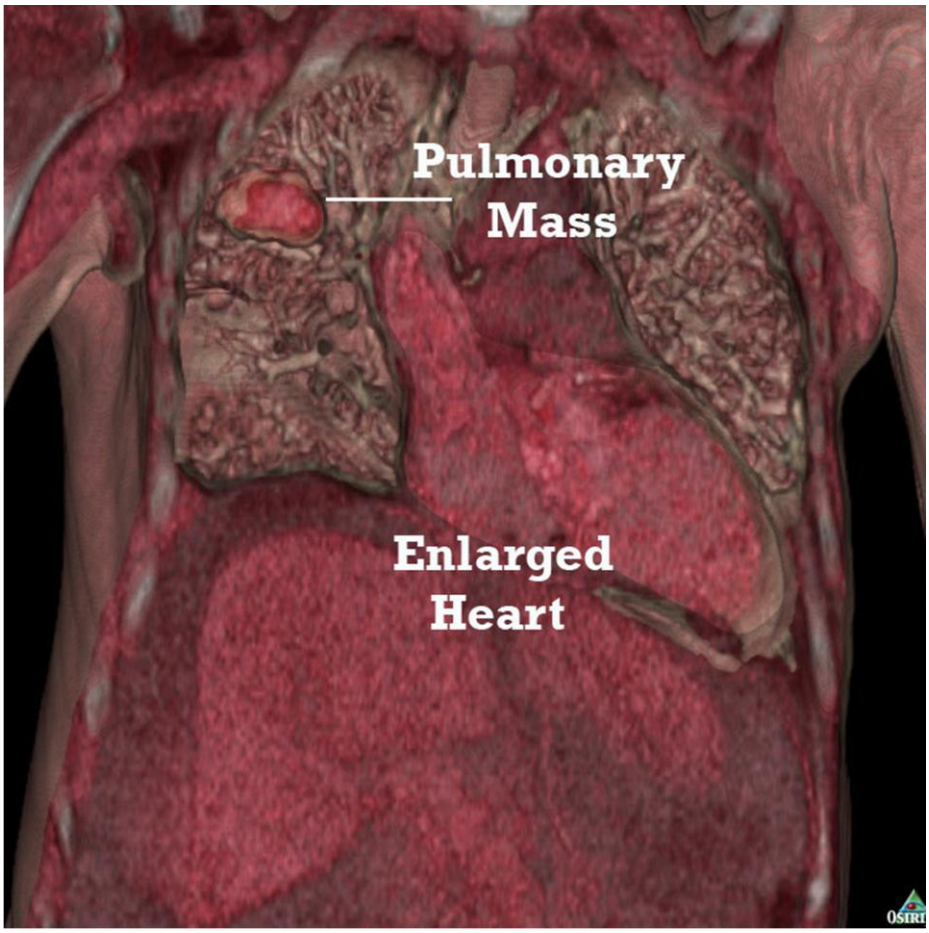

Figure 7A. Case K. Primary Tumor in the right lung. Reconstruction with Osirix-MD.

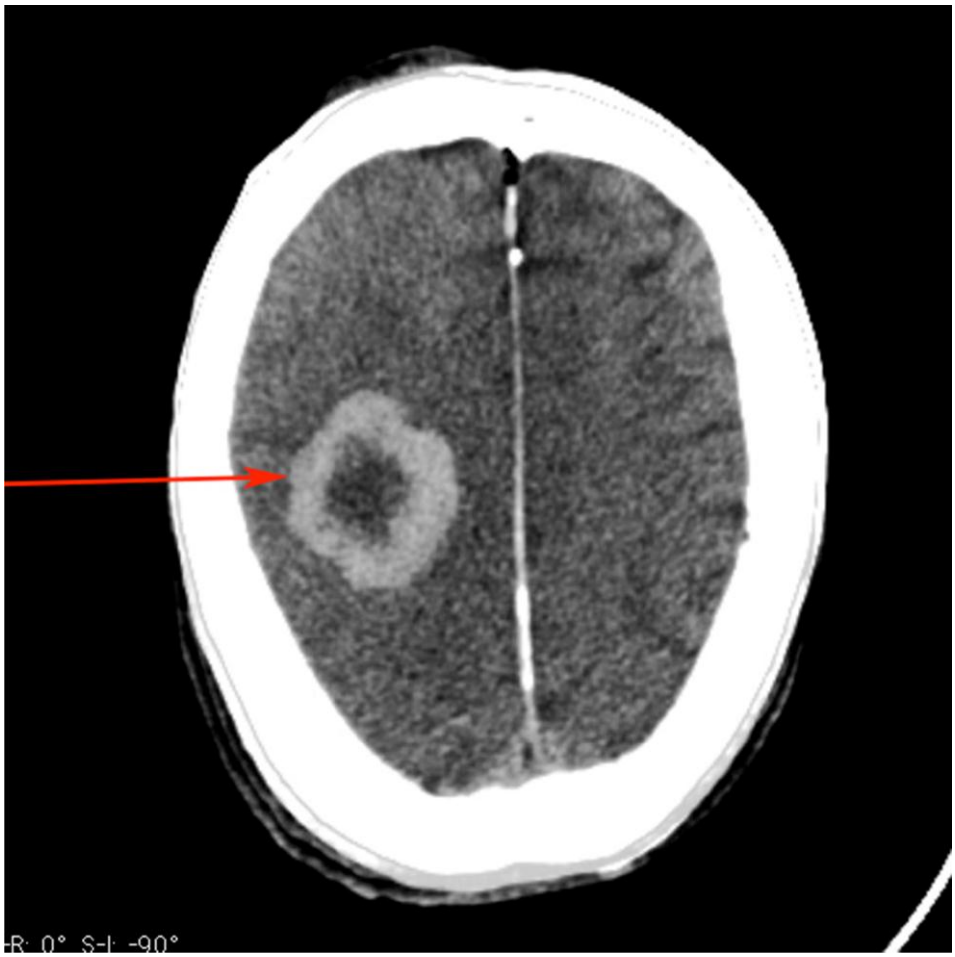

Figure 7B. Case K. Metastatic tumor from the lung in the right fronto-parietal lobe from the primary in the lung. CT image.

Q1.) What are you concerned about in a patient presenting with complaints of chest discomfort? A1.) In a patient with the above-mentioned symptomology it is always important to include a diagnosis including coronary artery disease (CAD) and potential for unstable angina/STEMI, pneumonia, pulmonary embolism, pericarditis, carcinoma, aortic dissection, pneumothorax and costochondritis.

Q2.) Which of the above are considered the 5 "can't miss" diagnoses in chest pain? A2.) The 5 "can't' miss" diagnoses in chest pain include: 1.) acute coronary syndrome (ACS), 2. pulmonary embolism (PE), 3.) aortic dissection 4.) pericarditis 5.) pneumothorax. All the above need thorough and evaluation and workup if suspected, the mentioned five are clinical emergencies and need emergent evaluation.

Q3.) Which of these diagnoses are more likely in this patient's presentation? Do you feel the patient needs emergent admission to the hospital? A3.) Given the timeframe of 2 months with worsening over the past three weeks, emergent etiologies are less likely and other pathology should be pursued. In this patient's case, we would want to consider pneumonia, carcinoma, costochondritis or muscle strain.

Q4.) What is the next best initial step? A4.) You refer the patient for chest XRAY and schedule a follow up appointment in one week to review the imaging. Chest X-ray is the preferred initial evaluation tool due to its low cost and low radiation in comparison to CT imaging. Upon reviewing the film, the patient was found to have a mass in the right lung and a 3cmx4cm mass centrally located within the right middle parietal lobe (Figure 7B.).

Q5.) What are you concerned about now? A5.) At this time, greatest concern is for either a lung carcinoma, pneumonia, empyema or lung granuloma (from systemic diseases such as sarcoidosis). However, benign lung nodules are found in the public and should always be included in one's differential.

Q6.) What should you do next? A6.) As mentioned above, benign lung nodules can be present in healthy adults. That said, assuming that a nodule is benign without further investigation would be mis-management and non-ethical. The next step in evaluation of this patient would include chest CT evaluation. The patient receives chest CT one day after their follow up appointment which reveals the following image- Figure7A.

Q7.) What features are suggestive of a benign vs. malignant mass? A7.) Benign mass qualities include a well-differentiated mass, that is generally <3cm, away from pleural tissue, capsulated and circumferential. Well comparing repeat chest imaging, slow growth additional supports a benign mass. Malignant features include a fast growing, spiculated, larger mass, without capsule, suspicion for peripheral invasion, and may be associated with calcification.

Q8.) Which type of malignancy comes to mind in this patient? A8.) Typically, if noting a centrally located malignant mass, small cell and squamous cell lung cancer are highest on the differential. Both may be associated with smoking however squamous cell has a much favorable prognosis in comparison to small cell's aggressive nature. Peripherally, malignant masses tend to include adenocarcinoma as well as large cell carcinoma. This patient's mass is centrally located and given their smoking history, most likely is squamous cell carcinoma. Biopsy of the mass is the only way to establish the definitive diagnosis.

Comment: This patient was a heavy smoker for many years and had been advised at many meetings with her doctor to stop her heavy smoking that initially resulted in a tumor in the right lung followed within a year or so by a metastatic lesion into the right temporal lobe. With the major decrease in smoking over the last several decades there has been a marked reduction in these cases. This patient was not considered for the neurosurgical removal of the tumor, but underwent chemotherapy and radiation without any success and eventually died from this tumor. The National Cancer Institute of the NIH has much information on the causes of cancer and its treatment while the National Brain Tumor Society is committed to better treatments and ultimately a cure for all brain tumors. (braintumor.org).

4)TRAUMA

Traumatic Brain Injury (TBI), Subdural, Case AS. (Figure 8A, 8B). You are the on-call neurology attending over the weekend and awake to a phone call at 3am. An on-call physician at a local nursing home is calling you regarding a resident and is concerned about her current mental status; the physician's report is as follows: Mrs. AS. is an 88y/o female with a past medical history including late onset Alzheimer's dementia (occasionally requiring treatment for psychosis), hypertension, hyperlipidemia, type 2 diabetes Mellitus, hex of squamous cell carcinoma s/p resection and ovarian CA. The patient was

reportedly at their normal baseline of AOx1 during the prior day and was assisted to bed without any abnormal difficulty. At approximately 2:30am during morning rounds, the night nursing assistant checked in on the patient who opened their eyes during inspection however did not appear to be off from their baseline. Approximately 15minutes later, a loud crying noise was heard from the patient's room with prompting further evaluation. On arrival, the patient was found to be on the floor, laying on their ride side. The patient was helped to their feet, consoled and assisted back to bed. She notably had experience urinary incontinence however otherwise no evidence of abnormality was appreciated. Brief physical exam revealed no clear wounds, abrasions or disfigurement, however the nursing home physician does comment on the patient's altered mentation and slurred speech, though notes a difficulty in assessing her given her baseline of AOx1 in the setting of dementia.

Q1.) What would you like to know next? What are you most concerned about now?

A1.) Now, there may be multiple explanations for the patient's altered mentation including dementia with psychotic symptomology potentially worsened by this episode, sundowning given the time of the day, pain related to a bone fracture or an intracranial hemorrhage. While the patient's current presentation may be confusing, it is of most concern and precedence to evaluate for the latter; intracranial hemorrhages.

Figure 8A. TBI, Case AS, 88 y.o. Gross appearance of the brain which was removed in the gross lab showing hemorrhagic infarcts in the cerebral hemispheres with extensive bleeding in the subarchnoid space.

Figure 8B. TBI, Case AS showing base of the brain with staining from bleeding around the brain stem.

Q2.) Do all patients who experience a fall re- quire brain imaging? A2.) The answer to this question is difficult however technically, no? Therefore, it is important to thoroughly evaluate each patient on an independent case- by-case scenario. Clinical indicators for head imaging in the setting of an unwitnessed in- clude confusion, bulbar symptomology in- cluding dysphagia and dysarthria, hemody- namic instability, unilateral weakness or sen- sory changes or loss of consciousness. Elderly age (>60 y/o), history of intracranial bleeds, concurrent anticoagulation or anti-platelet use or evidence of extracranial trauma should be strongly considered when evaluating these patient's. When in doubt, a head CT scan should be performed and is often the automat- ic approach performed by physician's in the setting of such a fall. In this case the CT would reveal an extensive skull fracture.

Q3.) What types of intracranial hemorrhages can a patient experience? A3.) Patients may experience epidural, subdural, subarachnoid or intra-parenchymal hemorrhages. You ob- tain additional information regarding the pa- tient's case and decided to recommend a CT scan. Upon arrival to the nearby emergency department, the patient is noted to be lethargic and no longer crying. GCS is calculated as an 8 and the patient is subsequently intubated for airway protection. Notable exam findings re- veal a dilated left pupil. The patient is brought emergently to the scanner where the radiologist confirms a left subdural hemorrhage

Q4.) What is a subdural hemorrhage and what are causes of this type of hemorrhage? A4.) A subdural hemorrhage is an intracranial bleed that collects within the dura and arachnoid space. Common etiologies include trauma (10-20% of all cranial trauma cases) as well as shaken baby syndrome. In the elderly pop- ulation (60-80y/o), patients with significant brain atrophy and large intracranial subarachnoid spaces appear to be predisposed.

Q5.) Which underlying vasculature structures are most likely associated with subdural hem- orrhages. What type of anatomical distribu- tion would one typically appreciated on head CT imaging? A) The most commonly associ- ated vasculature structures associated with

subdural hemorrhages are bridging veins which lie within dura mater and are suscepti- ble to tearing in the setting of trauma. When distinguishing a subdural bleed from other intracranial hemorrhages that may appear similar such as an epidural, it is important to look for a crescentic shape along the brain's surface which crosses the suture lines and may extend throughout multiple hemispheres. When comparing to an epidural hemorrhage, the patient will display a biconvex/lenticular shape which does not cross the suture lines.

Q6.) Why would you see a dilated right pupil in this case? A6) In this case with the intra- cranial bleed the dilated pupils are a sign of increased intracranial pressure (ICP) which is an emergency condition and would be re- sponded to by attempting to reduce the ICP. When considering the optic tract, it is im- portant to remember that about 40% of the optic radiation bypass the LGN and terminate in the midbrain in the tectum of the superior colliculus and the pretectal nuclei. The fibers from the tectum of the midbrain project back onto the visual nucleus of the pulvinar which then project onto visual association cortex, areas 18 and 19, that are important for volun- tary control of movements of the eye. In the midbrain, the Edinger-Westphal and ciliary nuclei are innervated by parasympathetic fi- bers. These bilateral pre-ganglionic parasym- pathetic fibers synapse in the Edinger- Westphal nucleus in the midbrain. These nerves subsequently project to the ciliary ganglion in the orbit which in turn innervate the sphincter pupillae to constrict the pupil and terminate on ciliary muscles for accom- modation.

Comment: Everyone is at risk for a traumatic brain injury (TBI) and it is most common in children and the elderly (21). The presence of seatbelts in automobiles, and better protective gear for players of contact sports including baseball, football, hockey, lacrosse, and soc- cer have reduced chronic traumatic encepha- lopathy (CTE), but there are still too many cases. (concussion foundation.org). Although the nursing home was continually monitoring this patient, sometime in the night she tried to get out of bed unassisted, fell and hit her head. She had a severe skull fracture with re- sultant intracranial hemorrhages and contu- sions to the brain which was ultimately fatal.

DISCUSSION.

The goal in our study was to use cutting-edge medical imaging technology to create VP that demonstrate the anatomical and pathological findings in cases that demon- strate many of the common causes of death as reported by the CDC [21] and then to make them available to further the education of our medical students, interns and residents. To undertake this study, we were dependent upon the availability of the CT scanner which can be especially heavily booked with in-house and ER patients. however, we were most for- tunate in that we had a collaboration with the staff in the Department of Radiology at the Tufts Medical Center to help us. By undertak- ing CT imagery on the bodies prior to their dissection we did more fully determine their medical history as radiological analysis of- fered more information than "cause of death " could ever offer. We developed the anatomi- cal and pathological models using the OsiriX image processing application [26] on a Mac Pro desktop or on a Mac Pro laptop. We found this program very easy to use. OsiriX and is available open source or for a fee as OsiriX- MD. We have found OsiriX-MD to work much better in developing our models.

The motivation for our development of virtual patients from cadavers comes from the Visible Man and the Visible Woman [27-29], and websites www.med.Biquitous;

www.virtualpatients.eu: [25]). The first Visi- ble Human data set was released from a male in 1994 at the National Library of Medicine (NLM) which is a high-resolution, multi- modal, full-body scans of two individuals who donated their bodies to science and they are available for research and medical educa- tion. The bodies that were sectioned and de- veloped into Virtual Humans include a 39- year-old male Visible Male [35] convicted murderer, executed in Texas by lethal injec- tion, and from a 59-year-old woman (Visible Female [35]) who died of a heart attack. The- se subjects formed the Visible Human Project, the world's first computerized library of nor- mal human anatomy which at their release time were too large sets of data for most com- puters. Since the mid 1990's these image sets have proven to be invaluable resources in the development of computer-based virtual ca-davers and patients. Through continued funding from the NLM, suites of visualization software toolkits have been developed allow- ing the user to build both 3D volumetric and surface models from the Visible Human Pro-ject image data. The results have been the de- velopment of many education-based products such as the *Interactive Series of Human Anat- omy* (Primal Pictures, London) and the *VH Dissector* (Touch of Life Technologies) for the teaching of normal human gross anatomy. Hilbelink [30], Graser et.al, [15], have done much work with VP and noted the develop- ment of a virtual patient is highly dependent upon the availability of both a high level of computing capability and a detailed set of da- ta from which to construct the virtual model, and we were fortunate to have that capability.

So why image cadavers, and what does one do with these CT images, and does it help in teaching Gross Anatomy? Cadavers form an integral part of medical education and we believe that the information gathered in the gross lab is unique and should be preserved in a digital form to further the education of our students [1]. Our plan was to pre-image all the cadavers prior to beginning the dissection and in several cases, we have found it possible to do a small sample and the students who had the pre-imaged bodies found this approach very informative and more engaging. Howev- er, with the unpredictability in acquiring ca-davers, and the continued shortening of time in the curriculum for Gross Anatomy, and fi-nally getting time on the CT, the reality is that there is not enough time to develop many of these virtual patients and make them available at the "bedside" in the Anatomy Lab for all our students. Instead we plan to create a data- base from the collected images and make it freely available.

We reported in our previous publication [3 & 4] that our students were given the op-tion of reviewing each Virtual Patient and an- swering the questions developed for each case even though they were not required to review the cases and 59 of 172 (34%) students accessed and reviewed the cases and images. They found these cases on the nervous system enlightening especially with the study ques- tions and the presentation of very representa- tive examples of disease within the CNS. With the VPs being created close to the end of the semester it was not possible to conduct a complete evaluation, however many students reported that the review of the VPs was useful and they encouraged us to continue develop- ing the VP. In further discussion with our stu- dents, they indicated that another limiting fac- tor in reviewing these VP was that they con-sidered this an inordinate amount of material added into what they already considered an excessive volume of required content for the Human Anatomy Course. Since these prelim- inary student reviews, we have found over the last few years that

many of our students once they are in their pathology found in each of our clinical years now access the- se VP and find them very useful, and they suggested that we either develop a few new cases each year for the course or continue to work up what we have and make it available as part of the medical curriculum

We have demonstrated in the VPs we developed that the listed Cause of Death for each patient is not an accurate description of the cadavers primarily due to their advanced age. The CT imaging demonstrates many pathological findings that are not listed for each patient due to the HIPAA laws, however the medical imaging technology is at a point that it can provide us with detailed morphological information on an individual patient which our team used for the development of VP with anatomically accurate models. We have also noted that adding air at the end of the em- balming process permits one to demonstrate the arterial system in each cadaver which our students also find very helpful (Figure One.). The development of these virtual patients can extend indefinitely the value of one's Ana- tomical Gift Program beyond a one-time laboratory dissection by storing the VPs on a secure server [4] and thus making them accessible to one's medical students. These VPs also better prepare our medical students for their dissection and early in their careers they learn to read and interpret these CT and MRI images, and are better in engrossing our stu- dents in studying anatomy. By including in- ternet links for each VP with appropriate cross references from reliable open sources such as NIH, Medline Plus.com, Answer.com or Mayo Clinic, com databases, the students readily obtain even more useful information on any disease.

There have even been some suggestions that the Visible Human might eventually replace cadavers as suggested by Dr. Donald Lindberg, the NLM director [31]. We believe that our development of Virtual Patients from cadavers with many neurological conditions makes a Gross Anatomy course even more relevant in a student's education by early in their training identifying the normal and pa- thology seen in CT or MRI images, and one can then even discuss how one might have treated the disease. The addition of a self- assessment quizzes to each case furthers the educational goal by blending the basic science and clinical material.

We have found many different venues to use for these VPs including paper cases, placement of the VP on a website, and the development of a video from the stack of CT images. Medical, dental students, and other health care students who access these VP are especially attracted to the videos with their running commentary on the anatomy and pathology in each patient, and labeled anatomi- cal structures. One of the most effective uses of our VPs is best demonstrated when a stu- dent sits down in front of a computer and simultaneously opens more than one case and our students in this setting are readily able to identify pathological findings simultaneously in several cases and compare the effects of different diseases.. We have used these VP cases to develop a database, and, we will continue to place them upon the secure server TUSK at Tufts Univer- sity School of Medicine or braindementia.net making it possible for students anywhere to access these images via the internet with ei- ther a computer, a smart phone or a tablet. Our goal is to expand our data base by adding in living patients with infectious diseases, including malaria, HIV/AIDS, TB, and additional traumatic injuries. The presence of the- se patients would be approved by an IRB and de-identified.

Simulators have emerged as a preferred training environments due to both practical and ethical reasons *[16, 30-35]*. We believe that the images collected from a cadaver

can also be turned into effective simulators demonstrating many pathological conditions with surgical implications and we are plan- ning to develop such a system using haptic techniques.

Notes on Contributors:

Samuel S Giles, MD, resident in Neurology at the University of Florida Medical Center in Jacksonville. Florida. He wrote up the cases for the Virtual Patients and developed the videos seen in this paper and continues to be active in developing additional VP.

Stanley Jacobson, PhD, Professor, Depart- ment of Integrative Physiology and Pathobi- ology. Tufts University School of Medicine, Boston Massachusetts and a Fulbright Schol- ar. He organized the imaging of the cadavers and assisted in writing up the VP cases. He teaches Gross Anatomy and Neurosciences to Medical and Dental students and undergradu- ates.

Eileen A. Mc Garry is an undergraduate ma- joring in Biology at Tufts University and helped in the development of the 3D anatomi- cal models which accompany the VP.

Joseph F. Polak, MD, MPH. Professor of Ra- diology, Tufts University School of Medicine and Tufts Medical Center, Boston Massachusetts. He developed the CT protocols we used in this project and he reviewed the DICOM images that we developed into anatomical models.

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Jennifer Sites and Jessica Fields from the De- partment of Radiology at Tufts Medical Cen- ter imaged the bodies.

John Gentile embalmed the bodies used in this study.

Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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