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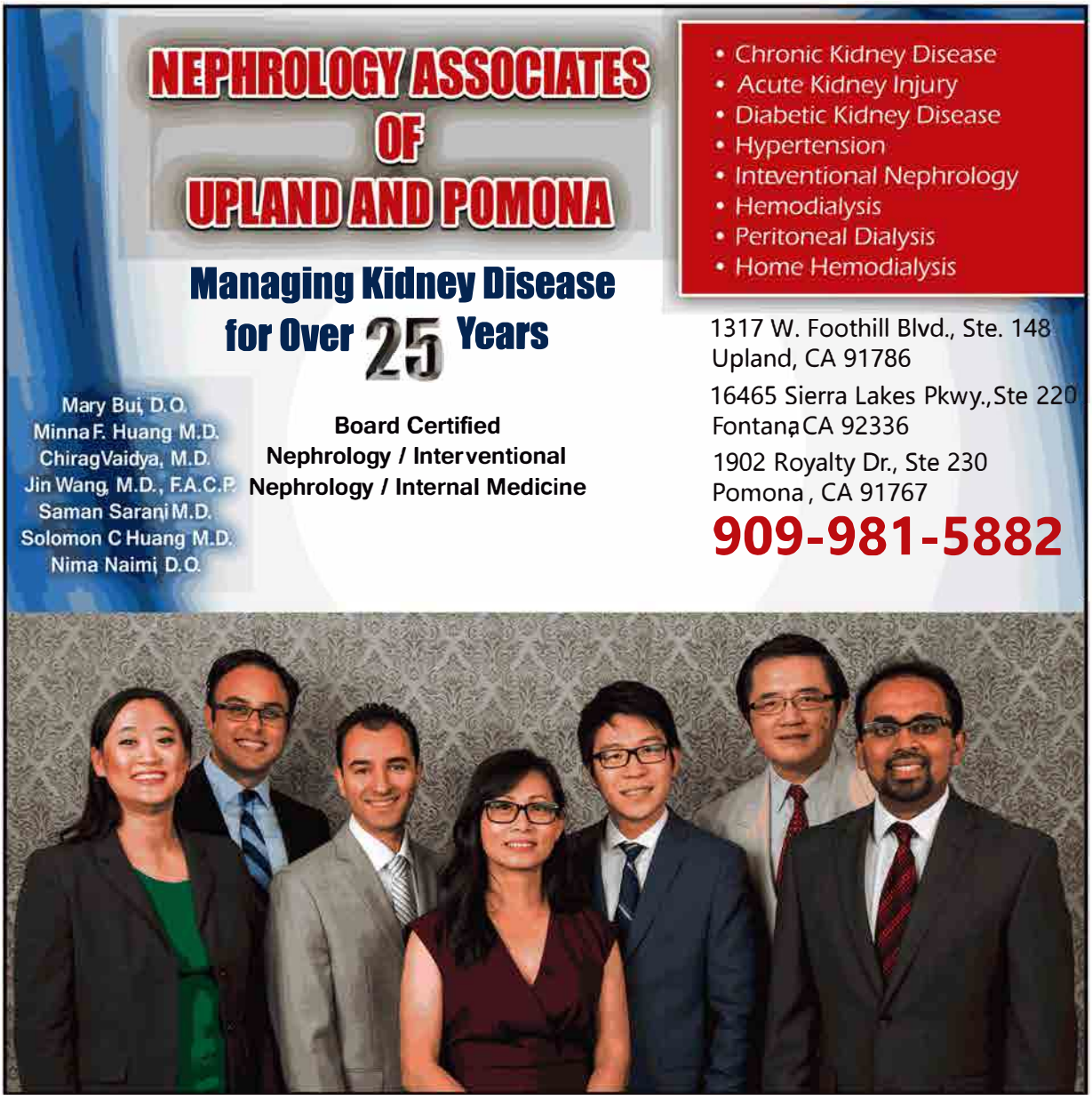

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Southern California Clinicians was established by the Medical Staff of Pomona Valley Hospital Medical Center in Pomona, California. It provides a journal for modern California clinicians to publish articles to share their clinical experiences and opinions with other physicians, show their academic achievements in medical practice, and keep a permanent record of valuable case studies and case reports from all departments and all specialities in the modern era.

This journal invites all clinicians in southern California to contribute interesting articles and reviews, including new developments in clinical skills and techniques, or new procedures applied during their medical practice.

In order to maintain the highest quality, accuracy and academic dignity, we reserve the right to peer review all articles. Articles will be reviewed by our editorial board and special consultants.

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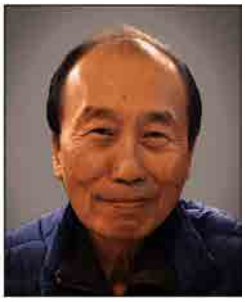
Guidelines for Authors

On behalf of the editorial staff of the medical journal *Southern California Clinicians*, I would like to extend an invitation to you to contribute articles for publication. Articles that pertain to your medical practice, any case reports you may have, or your past clinical experiences are welcome. Articles for publication in the 2017 edition are due no later than June 30th, 2018.

1) Use a single page to show your full name, your academic degrees and affiliations, and your current address, phone number, fax, e-mail.
2) All articles must be titled.
3) Please write your article with Microsoft Office Word, double spaced.
4) Length is flexible, from 1 page to 10 pages.
5) You may include a short abstract and conclusion as you wish. Slides, tables, figures, photos or pictures are welcome. Most important is a list of references numbered in the order in which you marked in the text.
6) All articles have to be original, never been published before, reflecting your own experience, knowledge and opinion.
7) All articles, once accepted, will be peer reviewed, corrected or revised and will be sent back to you for your approval.
8) Please submit all articles in both Microsoft Word format and pdf format by email to Yin H. Lai, M.D. at his email address: yinhlai@gmail.com

Preface for 2017 Edition

Yin H. Lai, M.D.
Editor-in-Chief



" One World – One Medicine – One Health " --- from CDC

Do you know?

October 15 to 21, 2017 was "International Infection Prevention Week". We have an article (by Dr. David Ha et all) which introduces a program regarding antibiotic stewardship and infection prevention at PVHMC.

November 3, 2017 was "One Health Day" conducted by CDC. The basic concept is that: to reach the goal of "Complete Health Care", the entire world needs collaborative efforts to provide a comprehensive care of human, animals and environment. Please read the article "The Importance of One Health Perspective….." (by Professor Selnow et all).

All articles in our 2017 issue are written by outstanding professors and clinicians from PVHMC, SARH, CASA COLINA HOSPITAL, UCI, UCLA, USC, UCRiverside, Western University, Cedars-Sinai, City of Hope, San Francisco State University, Harvey-Mudd, Keck Graduate Institute and Claremont Graduate University…).

All articles are strictly peer reviewed by enthusiastic specialists and editorial board members. I appreciate all supporters, as listed on page 2. who make this academic journal grow, continue to introduce newest medical knowledge, functioning as a proceeding to record annual achievements of local hospitals, providing an opportunity for clinicians to publish articles, and functioning as a teaching tool for medical students and residents in training.

The famous American educator Mark Hopkings wrote :

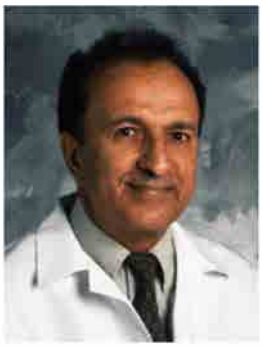
" Climb High, Climb Far; Your Goal, the Sky; Your Aim, the Star".

The Medical Journal of Southern California Clinicians says:

" Our Mission : One Health
Our goal: Universe
Our Aim: Human, Animals and Environment".

EBV-POSITIVE PLASMABLASTIC LYMPHOMA PRESENTING AS A RECTAL MASS IN AN HIV-POSITIVE PATIENT

A Case Presentation and Review of Literature



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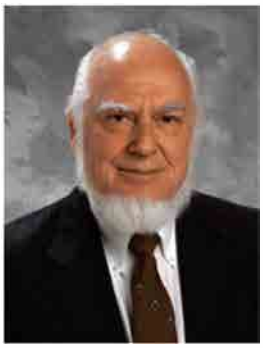

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keyword: rectal plasmablastic lymphoma, EBV associated lymphoma, HIV-associated lymphoma

ABSTRACT:

Gastrointestinal tract is the most common site of extranodal lymphomas, comprising approximately 15-20% of all lymphomas. The most common site of involvement is the stomach followed by small intestine. Rectal involvement by lymphoma is relatively rare and usually seen in the elderly or the HIV infected patients, especially with associated Epstein-Barr virus (EBV) infection.

CASE PRESENTATION:

A 39-year-old HIV-positive Hispanic male presented to the emergency department with symptoms of generalized weakness, fever, chills, and diffuse abdominal pain. He also complained of intermittent constipation and diarrhea with anal pain and blood in the stool of approximately one year duration. Five years ago, he noticed blood in stool and was treated as hemorrhoids. Ten days prior to admission at this hospital, the patient was seen at a local hospital due to losing weight and diffuse abdominal pain. The patient was scheduled for a colonoscopy, but he signed out of the hospital against medical advice.

At emergency department, a CT scan of abdomen showed a large rectosigmoid mass of 11 x 15 x 9 cm with partial obstruction (Figure 1). The mass was found to extend down the rectum and anus and compressed the bladder anteriorly.

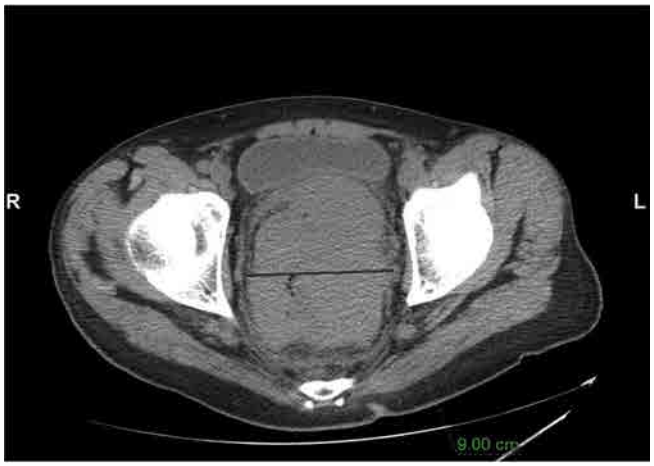

Figure 1. CT of the abdomen shows a large mass compressing on the bladder

On physical examination, the patient was a cachectic male in mild distress with sunken temples.
His temperature was 99° F, his pulse was 112/minute, blood pressure was 94/55 mm Hg, and respirations was 20/minute.

Laboratory findings included a CD4 count of 170/mm^{3,} white blood cell count of 4.9 X 109/L, and hemoglobin of 8.8 g/dL. Tumor marker studies including CEA and CA 19-9 were within normal limits.

A sigmoidoscopic biopsy showed colonic mucosa infiltrated by closely packed large malignant neoplastic cells with pleomorphic nuclei and significant mitotic activity (Figure 2). The initial differential diagnoses included poorly differentiated squamous cell carcinoma, large cell lymphoma, or other undifferentiated malignant neoplasms.

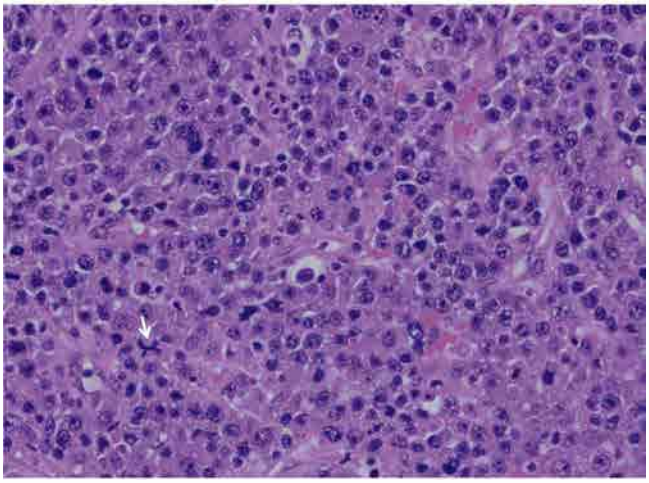

Figure 2. Biopsy of the rectal mass shows malignant lymphocytes with closely packed large nuclei, prominent nucleoli, and many mitotic figures, some with atypia (arrow).

Immunohistochemical stains were negative for cytokeratins, CD20, CD10, CD3, and CD5 as well as other usual lymphocytic markers. The neoplastic cells were however positive for CD138; EBER, a marker for EBV (figure 3); and Ki-67, a marker of cell proliferation, of virtually 100%. These histologic and Immunohistochemical findings argue against carcinoma and favor a diagnosis of EBV associated plasmablastic lymphoma*. Because of the significantly elevated proliferative index (Ki-67), MYC gene rearrangement was tested for evidence of amplification, which was positive. MYC gene belongs to the immediate early response genes, which are rapidly and transiently induced by RAS/MAPK signaling following growth factor stimulation of quiescent cells. It represents a potent oncogene.

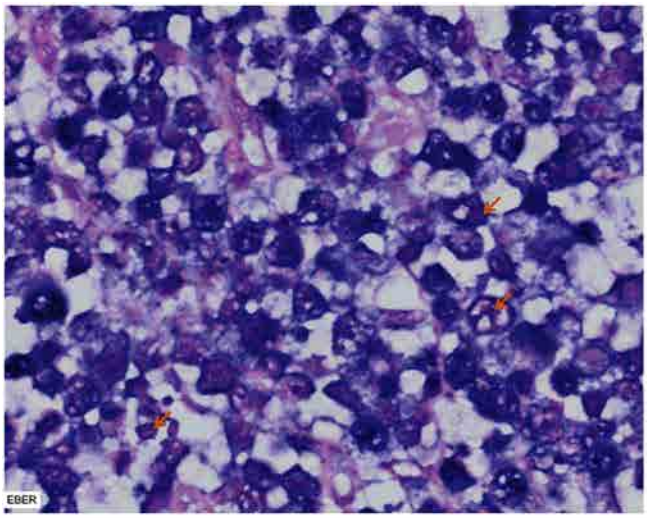

Figure 3. Immunohistochemical stain for EBER (marker for EBV), performed on a histologic tissue section of the rectal mass is positive (yellow arrows).

DISCUSSION:
Since the advent of anti-retroviral therapy (ART) there has been a significant increase in lifespan of HIV-infected individuals, but has led to an unintended rise in their malignancy-related deaths due to immunosuppression and advancing age[1]. Because of improvement in the CD4 count of patients on ART therapy there has, however, been a decreased incidence and risk for non-Hodgkin lymphoma [2]. Therapy with non-nucleoside reverse-transcriptase inhibitors (NNRTIs) and/or protease inhibitors (PIs) may have specially contributed to a decrease risk in these individuals from developing lymphoma, whereas the protective effect of nucleoside analogues alone was found to be inferior[8].

Non-Hodgkin lymphoma is more likely to be encountered in HIV-infected individuals with CD4 counts below 100 cells/μL. A French prospective cohort study involving 52,278 HIV-infected patients demonstrated that HIV-infected patients with CD4 counts less than 50 cells/μL had about a 15-fold increase in likelihood of developing NHL compared to patients with CD4 counts between 350-499 who were only two times as likely to develop NHL7. Individuals with a genetic component of protection via the CCR5-32 deletion tend to have a more favorable prognosis and are threefold less likely to develop an AIDS-related lymphoma[9].

The most common systemic NHL subtypes in individuals exposed to HIV are: Diffuse large B cell lymphoma (DLBCL, approximately 75 percent), Burkitt lymphoma (approximately 25 percent), Indolent B cell lymphoma (10 percent), Plasmablastic lymphoma (at approximately 2.6 percent), and T cell lymphoma (1 to 3 percent)[3]. Lymphomas of the gastrointestinal tract were found to be in 14 percent of those with AIDS-related lymphomas,

with less than 5 percent occurring in the liver, cecum, and rectum4. EBV has been detected in almost three-fourths of AIDS-related plasmablastic lymphomas. The WHO classifies plasmablastic lymphoma as a variant of DLBCL. Some immunophenotypic studies are, however, not supportive of this concept [18].

There is susceptibility of B cells to EBV infection in HIV-positive individuals due to impaired T cell immunity. EBV co-infection increases the risk of development of lymphomas in individuals with AIDS by the proposed mechanism of expansion of B cell clones (proliferation of clones of cells that have undergone alterations in oncogenes or tumor suppressor genes). Genes such as c-MYC and TCL1 oncogenes are susceptible to mutations in the setting of chronic B cell stimulation[12].

Plasmablastic lymphoma is an aggressive subtype of non-Hodgkin lymphoma , seen in HIV-positive patients, showing a strong correlation of co-infection with EBV [16]. Although rare, EBV-positive plasmablastic lymphoma should be a differential diagnostic consideration in patients with a history of immunodeficiency presenting with nonspecific symptoms of weight loss, abdominal pain, and rectal bleeding, especially in the presence of a rectal mass.

Plasmablastic lymphomas are generally associated with a poor prognosis and treatment options are limited due to the aggressive nature of this neoplasm. Reports in literature suggest that early clinical stage and complete response to chemotherapy with either CHOP, infusional EPOCH, hyperCVAD, and CODOX-M/IVAC are associated with a better outcome[15].

CONCLUSION:

We present a case of an HIV-positive 39-year-old male who presented with vague non-diagnostic symptoms of weakness, weight loss and abdominal pain referred to his thighs. On further questioning, he also complained of anal pain and bloody stools that were attributed to hemorrhoids. CT of the abdomen showed a large rectal mass which upon biopsy was diagnosed as EBV-positive plasmablastic Lymphoma. The latter should be included as an important differential diagnostic consideration in HIV or immune suppressed patients.

References:

1-Kaplan L., Wei Ai, Freedman A., Rosmarin A., et. al. AIDS-Related lymphomas: Epidemiology, Risk factors, and pathobiology. UpToDate Topic 4726 Version 20.0. Epub 2016 Nov 9

2-Biggar RJ, Chaturvedi AK, et.al. AIDS-related cancer and severity of immunosuppression in persons with AIDS. J Natl Cancer Inst. 2007 Jun 20;99(12):962-72. Epub 2007 Jun 12

3-Cote TR, Biggar RJ, Rosenberg PS, et. al. Non-Hodgkin's lymphoma among people with AIDS: incidence presentation and public health burden. AIDS/Cancer Study Group. Int J Cancer. 1997 Nov 27;73(5):645-50.

4-Diamond C, Taylor TH, Aboumrad T, Anton-Culver H., Changes in acquired immunodeficiency syndrome-related non-Hodgkin lymphoma in the era of highly active antiretroviral therapy: incidence, presentation, treatment, and survival. Cancer. 2006 Jan 1;106(1):128-35.

5-Clifford GM, Rickenbach M, Lise M, et. al. Hodgkin Lymphoma in the Swiss HIV Cohort Study. Blood. 2009 Jun 4;113(23):5737-42. doi: 10.1182/blood-2009-02-204172. Epub 2009 Mar 31.

6-Armenian HK, Hoover DR, Rubb S, Metz S, et. al. Risk factors for non-Hodgkin's lymphoma in acquired immunodeficiency syndrome (AIDS). Am J Epidemiol. 1996 Feb 15;143(4):374-9.

7-Guigeut M, Boue F, Cadranel J, Lang JM, et. al. Effects of immuno deficiency, HIV viral load, and antiretroviral therapy on the risk of individual malignancies (FHDH-ANRS CO4): a prospective cohort study. Lancet Oncol. 2009 Dec;10(12):1152-9. doi: 10.1016/S1470-2045(09)70282-7. Epub 2009 Oct 7.

8-Stebbing J, Gazzard B, Mandalia S, Teague A, et. al. Antiretroviral treatment regimens and immune parameters in prevention of systemic AIDS-related non-Hodgkin's lymphoma. J Clin Oncol. 2004 Jun 1;22(11):2177-83.

9-Dean M, Jacobson LP, McFarlane G, Margolick JB, et. al. Reduced risk of AIDS lymphoma in individuals heterozygous for the CCR5-delta32 mutation. Cancer Res. 1999 Aug 1;59(15):3561-4.

10-Gormley RP, Madan R, Dulau AE, Xu D, et. al. Germinal center and activated b-cell profiles separate Burkitt Lymphoma and diffuse large B-cell lymphoma in AIDS and non-AIDS cases. Am J Clin Pathol. 2005 Nov;124(5):790-8.

11-Biancotto A, Grivel JC, Iglehart SJ, Vanpouille C, et. al. Abnormal activation and cytokine spectra in lymph nodes of people chronically infected with HIV-1. Blood. 2007 May 15;109(10):4272-9. Epub 2007 Feb 8.

12-Yawetz S, Cumberland WG, van der Meyden M, et al. Elevated serum levels of soluble CD23 (sCD23) precede the appearance of acquired immunodeficiency syndrome-associated non-Hodgkin's lymphoma. Blood. 1995 Apr 1;85(7):1843-9.

13-Brahmania M, Sylwesterowic T, Leitch H. Plasmablastic lymphoma in the ano-rectal junction presenting in an immunocompetent man: a case report. J Med Case Reports. 2011; 5: 168. Published online 2011 May 3. doi: 10.1186/1752-1947-5-168

14-Alvaro-Lopez-Iniguez, Covarrubias M, et. al. Rectal Plasmablastic Lymphoma in HIV/AIDS: Two Cases. World Journal of Oncology, bimonthly, ISSN 1920-4531 doi: http://dx.doi.org/10.4021/wjon627w

15-Castillo JJ, Winer ES, Stachurski D, et. al. Prognostic factors in chemotherapy-treated patients with HIV-associated Plasmablastic Lymphoma. Oncologist. 2010;15(3):293-9. doi: 10.1634/theoncologist.2009-0304. Epub 2010 Feb 18.

16-Carbone A, Gloghini A, Larocca LM, et. al. Expression profile of MUM1/IRF4, BCL-6, and CD138/Syndecan-1 defines novel histogenetic subsets of human immunodeficiency virus-related lymphomas. Blood. 2001;97(3):744–571. doi: 10.1182/blood.V97.3.744.

17-Wong NA, Herbst H, Herrmann K, Kirchner T, et. al. Epstein-Barr virus infection in colorectal neoplasms associated with inflammatory bowel disease: detection of the virus in lymphomas but not in adenocarcinoma. J Pathol. 2003;201(2):312–318. doi: 10.1002/path.1442.

18-Vega F, Chang CC, Udden MM, Cho-Vega JH, et. al. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol. 2005 Jun;18(6):806-15.

Not Stumped: Surgical Management of Stump Appendicitis

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ABSTRACT:

Poor surgical management of primary appendicitis leaving an appendiceal stump greater than 0.5cm can result in re-inflammation and recurrent appendicitis. We report the case of a 62-year-old female with a 1-year history of intermittent right lower quadrant (RLQ) abdomnal pain 46 years after open appendectomy. The diagnosis of stump appendicitis was made by CT and laparoscopic completion appendectomy was performed. Stump appendicitis is a rare complication of appendectomy that must be considered in the clinical and surgical management of patients with RLQ abdominal pain with a history of previous appendectomy.

INTRODUCTION:

Appendicitis, or inflammation of the appendix, is the most common diagnosis leading to emergency abdominal surgery in the United States (1). The lifetime risk of developing appendicitis is 8.6% for men and 6.7% for women (2). Appendicitis classically presents as periumbilical pain that migrates to the RLQ abdominal pain and can present with associated with anorexia, nausea, and vomiting. Pain at McBurney's point, a positive Rosving's sign, positive psoas sign, and positive obturator sign can confirm the diagnosis.

While appendicitis is a clinical diagnosis, the advancement of imaging studies such as ultrasound (US) or computed tomography (CT) can help confirm the diagnosis. These imaging studies can help differentiate from other presenting conditions that mimic acute appendicitis. In performing an appendectomy, it is crucial to properly identify the anatomy before resecting the appendix. In this paper, we aim to discuss a rare complication of appendectomy – stump appendicitis.

CASE PRESENTATION:

A 62-year-old female presented to the emergency room with worsening RLQ abdominal pain. She had an open appendectomy performed 46 years ago and had a 1-year history of recurrent RLQ pain with intermittent nausea, vomiting, and diarrhea. She had a history of multiple visits to physicians who did not suspect appendicitis given her history of appendectomy. Her labs showed a total leukocyte (WBC) count of 6.4x109/L. A CT performed found a short approximately 3cm tubular structure arising from the cecal pole within the expected region of the

appendiceal stump with 3 moderate to large appendicoliths in situ measuring up to 1.5cm in maximum diameter.

There was associated moderate mural thickening in addition to minimal pericecal fat stranding and several prominent lymph nodes in the ileocecal area indicative of uncomplicated acute/subacute on chronic stump appendicitis. She was immediately scheduled for a laparoscopic complete appendectomy. Intraoperatively, the taenia coli was identified and followed down to the ileocecal region, where there was inflammation and adhesions from the previous surgery.

The area of inflammation was resected using a stapler and removed laparoscopically. Post-operatively the patient was observed overnight and her abdominal pain resolved. She was discharged after 1 day with mild incisional pain. The pathology report on the specimen confirmed an appendiceal stump with acute and chronic inflammation, congestion, and hemorrhage.

DISCUSSION:

Stump appendicitis (SA) is defined as re-inflammation of any residual appendiceal tissue after appendectomy (3). It has a reported incidence of 1 in 50,000 cases and can occur from 2 weeks up to 50 years after appendectomy (1,4). The presenting symptoms of SA are indistinguishable from those of primary appendicitis, however most clinicians do not consider recurrent appendicitis as a differential diagnosis for patients with RLQ abdominal pain after previous appendectomy (5). This is primarily due to a lack of awareness, as SA is not prominent in medical literature. Although the first documented case of SA was reported in 1945, several systematic reviews have found less than 100 reported cases in the literature (2-4).

Most commonly stump appendicitis is misdiagnosed as constipation, gastritis, or right-sided diverticulitis (4). The differential diagnosis can include Meckel's diverticulitis, Crohn's terminal ileitis, ureteric colic, cecal diverticulitis, or acute cholecystitis (6). A delay in diagnosis can lead to perforation with or without gangrene (5). The pathology of the appendiceal stump can vary widely to include infection, malignancy and hemorrhage (7).

The most common radiographic tests to confirm the diagnosis of stump appendicitis are ultrasound (US) and CT. US can reveal a thickened stump, inflammatory changes, fecalith, fluid in the right iliac fossa and surrounding stump, and edema of the cecum (2).

Abdominal CT is the gold standard for the diagnosis of stump appendicitis.To date, there are not enough cases of stump appendicitis to draw any conclusions regarding etiology (1). It is corroborated that stump appendicitis is highly unlikely with an appendiceal stump shorter than 0.5 cm (2). it is corroborated that SA is highly unlikely to occur in appendiceal stumps shorter than 0.5cm (2).

Leaving a longer stump may result in chronic inflammation or serve as a reservoir for fecoliths, thus the appendix is more prone to becoming ischemic and eventually perforate or suppurate (4). This can be avoided with proper surgery of primary appendicitis.

In both laparoscopic and open surgeries, it is essential for the surgeon to identify the appendicular base clearly before performing appendectomy. This can be done by tracing the taenia coli to the base of the appendix, or locating and ligating the recurrent branch of the appendicular artery that marks the appendicular base (3). If this is not possible with the laparoscopic approach, then conversion to an open procedure is mandatory (9). The use of stapling devices where the appendix can be stapled-off at its base leaving virtually no appendicular tissue at all is the mainstay in preventing the possibility of developing SA (3).

The treatment of stump appendicitis is a complete appendectomy. It is recommended to follow a laparoscopic approach guided by the CT findings (5). One of the greatest challenges of a complete appendectomy is identifying the stump, especially in the setting of chronic inflammation. The procedure is very similar to that of the initial appendectomy although extended resection may be required in the presence of extensive inflammation and peritonitis. Severe cases may require ileocecostomy to completely remove all the inflamed tissue (10).

CONCLUSION:

Stump appendicitis is a rare complication of appendectomy that usually arises in stumps greater than 0.5cm. The presentation of SA is similar to that of primary appendicitis – periumbilical pain that moves to the right ower quadrant of the abdomen, with associated anorexia, nausea, and vomiting. Diagnosis can be confirmed either by US or CT. Diagnostic delay can lead to perforation with or without gangrene.

The treatment is a completion appendectomy that identifies and removes the remaining inflamed appendix. Surgery is not indicated for incidental findings of an appendiceal stump (5). It is imperative that clinicians do not overlook the possibility of recurrent appendicitis when evaluating patients with prior appendectomy.

References

1.Aschkenasy, M. T., & Rybicki, F. J. (2005). ACUTE APPEN DICITIS OF THE APPENDICEAL STUMP. The Journal of Emergency Medicine, 28(1), 41-43.

2.Subramanian, A., & Liang, M. K. (2012). A 60-year literature review of stump appendicitis: The need for a critical view. The American Journal of Surgery, 2013, 503-507.

3.Kanoa, H., Al Samaraee, A., Nice, C., & Bhattacharya, V. (2012). Stump appendicitis: A review. International Journal of Surgery, 10, 425-428.

4.Hendahewa, R., Shekhar, A., & Ratnayake, S. (2015). The dilemma of stump appendicitis — A case report and literature review. International Journal of Surgery Case Reports, 14, 101-103.

5.Roberts, K. E., Starker, L. F., Duffy, A. J., Bell, R. L., & Bokhari, J. (2011). Stump appendicitis: A surgeon's dilemma. Journal of the Society of Laparoendoscopic Surgeons, 15, 373-378.

6.Hasmi, K. S., Wibberley, H., Ahmed, I., & Soares, L. (2013). Stump appendicitis: A relatively under-reported reality. BMJ Case Reports, 2013, bcr2012008449. doi:10.1136/cr-2012-008449.

7.Amesquita, M., & McGillicuddy, D. (2008). Recurrent appendicitis. Internal and Emergency Medicine, 3, 251-253.

8.Crocco, S., Pederiva, F., Zanelli, E., Scarpa, M., Barbi, E., & Ventura, A. (2013). Stump appendicitis seven years after appendectomy. Association of Paediatric Surgeons of Pakistan, 4(2), 33.

9.Leff, D. R., Sait, M. R., Hanief, M., Salakianathan, S., Darzi, A. W., & Vashisht, R. (2010). Inflammation of the residual appendix stump: A systematic review. Colorectal Disease, 14, 282-293.

10.Truty, M. J., Stulak, J. M., Utter, P. A., Solberg, J. J., & Degnim, A. C. (2008). Appendicitis after appendectomy. Archives of Surgery, 143(4), 413-415.

Aspergillus Vertebral Osteomyelitis – -- The Malignancy Mimicker

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Introduction:

It is known that immunocompromised patients can frequently contract fungal infections that result in increased morbidity and mortality (11). Fungal infection of the musculoskeletal system, including infection of the spine and intervertebral space, is uncommon. The most common cause of fungal infection is Candida after organ transplantation, therefore resulting in neutropenia (1). The most common etiologies of vertebral osteomyelitis include Staphylococcus aureus, Mycobacterium tuberculosis, followed by fungi. Among fungal infections

Aspergillus vertebral osteomyelitis in immunocompetent patients is even rarer, with only a few cases reported (3). Inhalation of Aspergillus conidia is a common precipitating event for infection. Historically inhalation of a large number of conidia, such as at a construction site, results in a high airway exposure and a higher incidence of infection. Normally patients on corticosteroids, solid organ or bone marrow transplant patients, or patients on immunosuppressive therapy are more susceptible to infection by Aspergillus species. Inhaled conidia are first encountered by phagocytes of the innate host defense, such as macrophages found in the lungs. These macrophages secrete inflammatory-inducing cytokines that recruit neutrophils after recognizing components of infectious conidia cell walls.

Neutropenic patients are unable to mount an effective response to the inflammatory mediators, resulting in uninhibited infection by Aspergillus species. Other factors that can contribute to the dissemination of

Aspergillus throughout the body include:
1) Suppressing T-cell response, 2) inhibiting macrophage phagocytosis and, 3) NADPH Oxidase defect (seen in chronic granulomatous disease). A defining characteristic of Aspergillus infection is vascular invasion, resulting in infarction and necrosis of body tissues. This is caused by fungi binding to blood vessel wall components such as the basement membrane or the extracellular matrix and cutting off the blood supply to structures distal to these blood vessels.

Of the Aspergillus species, A. fumigatus was the most common species resulting in infection. A study of 218 patients with Aspergillus infections found that 67% were caused by A. fumigatus, while A. flavus comprised 13%,

A. niger comprised 9%, and A. terreus comprised 7% (4). Infection can manifest in numerous body systems including the pulmonary, integumentary, cardiovascular, musculoskeletal, and gastrointestinal systems. Common symptoms consist of fever/chills, chest pain, shortness of breath, cough and/or hemoptysis. However, the absence of these symptoms does not rule out the possibility of infection by Aspergillus species.

Case Presentation:

Mr. MC is a 54-year-old male with a history of obesity, sleep apnea, and cervical degenerative spondylolisthesis who presented to the clinic for evaluation of blood lab abnormalities. His initial CBC consisted of WBC of 11.7 x 103 /μL, Hgb of 11.2 g/dL, platelet count of 415 x 103 /μL, MCV of 74 fL, MCH of 23.3 pg, and an absolute neutrophil count of 8760 cells/m3. His CMP was within normal limits with the exception of the total protein being 8.6 g/dL, an albumin of 3.5 g/dL, and a globulin of 5.1 g/dL His serum iron level measured 31 μmol/L, TIBC 238 μmol/L, iron saturation was 13%, and ferritin was 1945 ng/mL. Serum Protein Electrophoresis (SPEP) measured an M spike of 0.3 g/dL, erythrocyte sedimentation rate (ESR) was 106 mm/hr, rheumatoid factor measured 37 IU/mL, C-reactive protein measured 9.32 mg/L, and there was a negative anti-nuclear antigen. The patient also stated that he had had a 100-pound weight loss over the last year.

The evidence of microcytic anemia, an elevated ferritin level, and low TIBC was suggestive of an anemia of chronic disease with concurrent ongoing infection. Four months later, a follow-up lab showed M protein spike of 0.4 g/dL, WBC 13.5 x 103 /μL, Hgb 10.3 g/dL, platelet count of 473 x 103 /μL, and absolute neutrophil count of 10,166 cells/m3, GFR of 42 ml/min/1.73m2, BUN of 54 mg/dL, and creatinine of 1.8 mg/dL. Serum calcium levels were within normal limits. Immunofixation showed presence of IgG lambda monoclonal band. The patient was seen by his nephrologist. Ultrasound of the bladder and kidneys showed no significant finding. The bone scan showed numerous thoracolumbar compression fractures consistent with metastatic disease, multiple bilateral healing rib fractures with cervical spondylosis. A CT scan of the chest, abdomen, and pelvis without contrast showed negative except diffuse sclerosis fishmouth deformities and multifocal compression fractures in the thoracolumbar spine at multiple levels. A bone marrow biopsy showed slightly hypercellular marrow but normal tri-lineage hematopoiesis. There was also markedly increased iron stains noted and increased atypical megakaryocytes. Subsequent flow cytometry did not find any phenotypic evidence of leukemia or lymphoma. A screening for serum free light chains was not completed due to the fact that a bone marrow biopsy was already obtained, and the negative result did not warrant further multiple myeloma workup. Jak 2 and Calretinin mutation analyses were completed to confirm if a myeloproliferative disorder was the cause of the patient's symptoms. Both analyses were found to be negative. The patient continued to be monitored with periodic CBC and CMP. These tests showed WBC 18.5 x 103 /μL, Hgb of 10.6 g/dL, platelets of 620 x 103 /μL, ANC of 14,504 cells/m3, sodium of 132 mEq/L, K+ of 3.3 mEq/L, albumin of 3.2 g/dL, and globulin of 4.9 g/dL. The lab values showed increasing leukocytosis, anemia, thrombocytosis, and electrolyte abnormalities. The patient presented back to the clinic with debilitating back pain, so an MRI of the spine was ordered to assess for malignancy metastasis or bone lesions. Findings of the MRI were stated to be consistent with extensive metastatic disease throughout the lumbar spine and sacral and right iliac bone with multifocal compression fractures. There is also extension of the mass into the spinal canal and bilateral neural foramen, causing spinal stenosis and neural foraminal narrowing most severe at L2-3 and L3-4 levels.

At the next follow-up visit the patient was in a walker, had an additional 13-pound weight loss during the previous six weeks, appeared to have tetany, and reported loss of control of bowels. The patient was sent to the emergency room and evaluated by a neurologist. The neurological findings were consistent with cauda equina syndrome due to an epidural abscess. An abnormal MRI scan showed likely metastatic or possible lymphoproliferative disorder. The spinal mass was removed with L2-4 laminectomy and medial facetectomies. Grocott (or Gomori) methenamine silver nitrate stain (GMS stain) yielded a diagnosis of Aspergillus, which might have caused spinal compression fractures. The patient was started on Voriconazole and recent lab values were measured, with a Hgb of 10.4 g/dL, Hct of 32.4%, MCV of 77.6 fL, and a MCH of 24.9 pg. An MRI of the lumbar spine was done five months after the surgery and showed multilevel foraminal narrowing greatest on the right at L4-L5 and L5-S1 and greatest on the left at L4-L5. However, no significant central stenosis at any level was noted on the MRI.

Discussion:

The differential diagnoses for this case presentation included: Monoclonal Gammopathy of Undetermined Significance (MGUS), multiple myeloma, myeloproliferative disorders, Pott's disease, rheumatoid arthritis, and primary hyperparathyroidism.

IgG/A/M MGUS is defined as an asymptomatic premalignant clonal plasma cell or lymphoplasmacytic proliferative disorder that has the presence of a serum

monoclonal protein (IgG or IgA or IgM) less than 3 g/dL, and clonal bone marrow biopsy plasma cells less than 10% and no myeloma defining events, as mentioned previously in the CRAB and SLiM criteria (8). Since there were less than 10% blasts in the bone marrow biopsy and serum monoclonal protein is less than 3 (the patient had an M- protein band of 0.4 g/dL), this patient could fall under an MGUS diagnosis. It is possible that the patient had an underlying MGUS that was not related to the disease or its progression.

The next differential on the list was multiple myeloma. The Myeloma International Working Group's (IMWG) multiple myeloma's diagnostic criteria involves the following:

1) Clonal Bone marrow plasma cells equal to or greater than 10% or
2) Biopsy proven bony or extramedullary plasmacytoma and
3) 1 or more of the CRAB criteria, which includes:
    a. Calcium Elevation (>11 mg/dL or >1 mg/dL higher than upper limit of normal)
    b. Renal insufficiency (Creatinine clearance less than 40 mL/min or serum creatinine greater than 2 mg/dL)
    c. Anemia (Hemoglobin less than 10 g/dL or 2 g/dL < normal)
    d. Bone Disease (One or more 1 lytic lesion on skeletal radiography, CT, or PET-CT).
    or
4) 1 or more of the SLiM criteria, which includes:
    a. Clonal Bone marrow plasma cells greater than or equal to 60%
    b. serum free light chain ratio involved:unin volved greater than or equal to 100 (provided involved free light chain levels are at least 100 mg/L or higher)
    c. MRI showing more than one focal lesion (greater than or equal to 5 mm each) involving the bone or bone marrow (8).

The mild M-protein spike, elevated total protein, and IgG lambda monoclonal bands shown on immunofixation studies were initially suggestive of multiple myeloma, however these are not listed as part of the diagnostic criteria. The patient did have multiple bone lesion involvements shown on MRI. However, he did not match the CRAB criteria or the SLiM criteria. This was because his calcium was within normal limits, GFR was 42 and Creatinine was 1.8, Hemoglobin was always above 10, and clonal bone marrow plasma cells were within normal limits. The bone marrow biopsy did not show evidence of at least 10 percent of plasma cells, and thus does not match the criteria for multiple myeloma. Myeloproliferative disorder is a broad spectrum of different diseases, which includes: Essential Thrombocythemia (ET), primary myelofibrosis (PMF), polycythemia vera (PCV), and chronic myelogenous leukemia (CML).Myeloproliferative disorder is a broad spectrum of different diseases, which includes: Essential Thrombocythemia (ET), primary myelofibrosis (PMF), polycythemia vera (PCV), and chronic myelogenous leukemia (CML). Myeloproliferative disorders can cause bone lesions, as well as weight loss and fatigue. However, these aforementioned myeloproliferative disorders are less likely for the following reasons:

1)PCV would be less likely in this patient due to the history of anemia instead of polycythemia.
2)CML is less likely in this patient as well based on the negative bone marrow biopsy, the lack of clonal proliferation of WBCs in cytometry testing, and a lower than expected leukocytosis.
3)Primary myelofibrosis is less likely because of the lack of splenomegaly on physical exam and CT imaging, and the lack of myelofibrosis noted on bone marrow biopsy.

In addition, Calreticulin (CALR) exon 9 mutation and JAK 2 mutation tests were both negative in this patient. However, according to the revised WHO diagnostic criteria for PCV, ET, and PMF, these disorders are not a static but not continuous spectrum, and absence of disease does not necessarily rule out the disease (9). Tuberculosis can occur outside of the lungs and involve the vertebral bone, and this is known as Pott's disease. Tuberculosis of the bone can lead to bone degeneration and deformity, which may lead to cauda equina syndrome (2). Pott's disease is usually a complication of tuberculosis in immunocompromised adults. However, with a negative CT scan of the lungs and a negative AFB stain of the epidural mass that was excised, tuberculosis is a less likely.

Rheumatological diseases such as Sjogren's syndrome and systemic lupus erythematosus can cause elevation of the M-protein spike, along with other inflammatory markers such as rheumatoid factor and ESR, as was seen in the patients lab results. The inflammation that is caused by these diseases can lead to inflammation of the bone and cause sclerotic changes. This presents similarly to osteomyelitis on imaging. Having said that, besides the rheumatoid factor, all other Lupus 12-panel markers came back negative, making a rheumatological cause less probable.

Lastly, primary hyperparathyroidism can cause bone lytic lesions that can present similarly as they did in the patient's case. However, based on the normal calcium, PTH lab values, and negative DEXA scan, this made primary hyperparathyroidism less likely of a cause. Based on the rapid progression of fecal incontinence and

lower extremity neurological abnormalities, numerous multifocal compression fractures and bilateral spinal foramina stenosis on MRI imaging, and positive GMS fungal stain with fungal hyphae suggestive of Aspergillus species; the patient was diagnosed with cauda equina syndrome secondary to Aspergillus vertebral osteomyelitis and epidural abscess. GMS fungal stain is considered the standard diagnostic tool for Aspergillus identification, and Aspergillus typically appear as thin septal hyphae with acute angle dichotomous branching (5). The aforementioned description of aspergillus spp was consistent to what was found in the surgical pathology report of the L2-L4 epidural mass. The Aspergillus epidural abscess caused extensive enough compression of the nerve roots that it resulted in cauda equina syndrome.

This was consistent with the fecal incontinence, as well as the neurological abnormalities of hip flexor and quadriceps weakness and absent knee deep tendon reflexes. Many indications from the imaging and initial lab findings pointed towards malignancy as the root cause of bony changes, anemia, and acute renal failure. However, through numerous negative findings from follow-up tests and the definitive epidural mass biopsy, the culprit was of an infectious rather than neoplastic nature. The patient had no past history of IV drug use, smoking, alcohol abuse, previous spinal or lumbar puncture procedure, and was never deemed immunocompromised based on previous CBC labs. The patient used to work at a nuclear plant and his father has had a history of tuberculosis exposure; however the source of the Aspergillus infection that lead to the vertebral osteomyelitis and epidural abscess is unknown. A study found that patients most commonly acquired aspergillosis from a hematogenous infection, although about one fourth of the patients obtained the infection from a spinal procedure (10). Data from a case study reported approximately 30% of patients with Aspergillus vertebral osteomyelitis were immunocompetent (6).

Prognosis and survival of patients with Aspergillus vertebral osteomyelitis is not well- studied due to the rarity of its occurrence, but a review done by Vinas et. al in 1999 stated that in immunocompetent patients, the mortality rate was approximately 30% and the recovery rate was around 68.3% (11). However, since the emergence of many different antifungal therapies, other more recent studies have reported a mortality rate of 20% (10). Patients with paraplegia tended to have poorer outcomes than those that did not have such significant neurological damage.

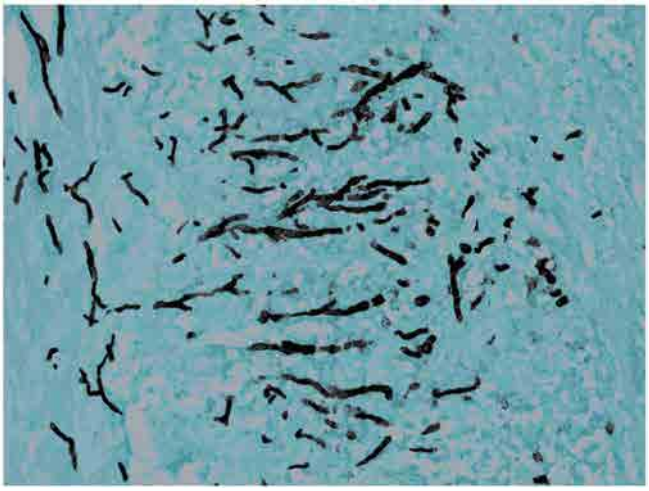

Figure 1: AMS stain of MC's L2-L4 vertebral mass showing aspergillus species with septate hyphae and acute angle dichotomous branching

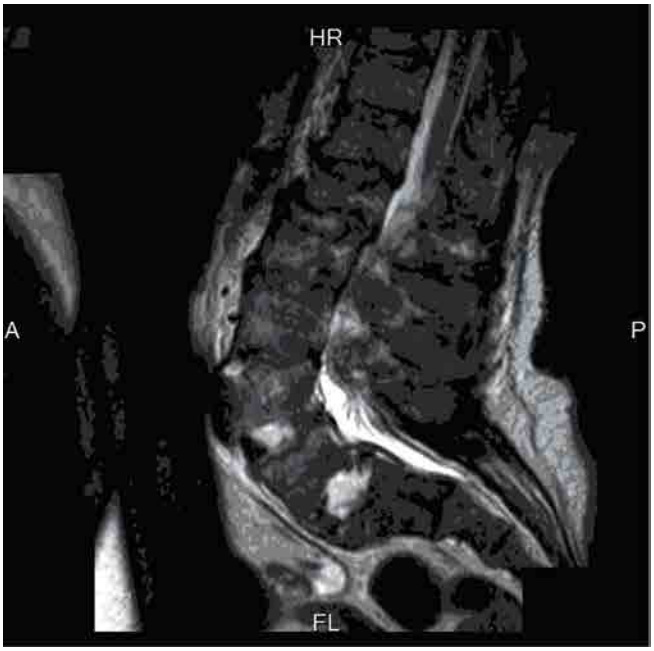

Figure 2: T2 weighted MRI of lumbar spine showing extension of mass into spinal canal at level of L2-L3 and L3-L4 and partial effacement of perineural fat

The data on the efficacy and outcome of treatments for Aspergillus vertebral osteomyelitis have been limited mainly to small case reports and studies. Despite this, Infectious Disease Society of America (ISDA) recommends either voriconazole or amphotercin for Aspergillus Osteomyelitis. Voriconazole has been demonstrated to be superior in treatment of invasive aspergillosis and is less toxic compared to amphotercin B (4). Voriconazole, along with other triazole agents, can be taken orally, and the plasma drug levels can be monitored and adjusted for safer and more effective treatment. The length of

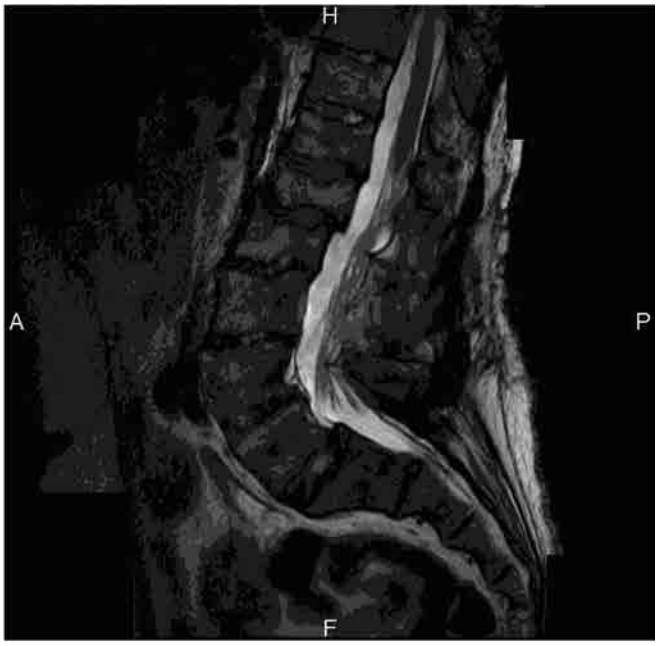

Figure 3: T2 weighted MRI of lumbar spine 5 months after L2-L4 laminectomy and medial facetectomies shows mild lumbar spondylotic changes at L4-L5 and L5-S1. No significant central stenosis, effacement of perineural fat, or mass with extension into spinal canal seen at any level

treatment has not been established, but ISDA guidelines states that the triazole agent(s) should be given for a minimum of 6-8 weeks in order to be effective, particularly in non-immunocompromised patients. A generous range of 1-12 months has been given as a broader therapeutic timeline. Most patients that have received Voriconazole in the Studemeister et al. study were able to tolerate the treatment, except for one patient who had a photosensitivity rash reaction (10).

Cauda equina syndrome is considered a neurosurgical emergency. Spinal decompression followed by a lumbar laminectomy and medical facetectomy of L2-L4 were necessary interventions to relieve the spinal compression caused by the epidural abscess. Both interventional neurosurgery and triazole therapy are crucial components in the recovery of the patient. Since the ferritin serum levels were elevated, iron supplementation would not be an appropriate treatment, as this would increase the ferritin levels further and cause an iron overload toxicity.

The fecal incontinence of the patient has since resolved and we will be monitoring the patient every 3 months with history, physical, and CBC and ferritin levels. As of December 1st, 2016, the patient's CBC panel was normal and his ferritin has decreased from 2990 ng/mL six months prior to this date to 930 ng/mL. The patient is to be on a 200 mg oral tablet of voriconazole triazole therapy for the next six to twelve months. He had already shown signs of recovery in his one month follow up by being able to ambulate more, cessation of his incontinence, and improvement in his anemia and white blood cell count.

References:

1. Frazier DD, Campbell DR, Garvey TA, Wiesel S, Bohlman HH, Eismont FJ. Fungal infections of spine.Report of eleven patients with long term follow up. J Bone Joint Surg Am. 2001;83:560–5.

2. Garg RK, Somvanshi DS. Spinal tuberculosis: A review. The Journal of Spinal Cord Medicine. 2011;34(5):440-454.

3. Govender S, Rajoo R, Goga IE, Charles RW. Aspergillus osteomyelitis of the spine. Spine (Phila Pa 1976) 1991;16:746–9

4. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole verus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med2002;347:408-415.

5. Hope WW, Walsh TJ, Denning DW. Laboratory diagnosis of invasive aspergillosis. Lancet Infect Dis 2005; 5: 609–22

6. Lin SJ, Schranz J, Teutsch SM .Aspergillosis case-fatality rate: systematic review of the literature. Clin Infect Dis 2001;32:358-366.

7. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoieticstem cell transplant recipients. Clin Infect Dis. 2002;34(7):909-17

8. Rajkumar SV, et al. Lancet Oncol. 2014;15(12):e538-548. National Comprehensive Cancer Network [NCCN]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guide- lines). Multiple Myeloma. Version 3.2016. Release date : 01/15/2016.

9. Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood 2008 112:231-239.

10. Studemeister A, Stevens DA. Aspergillus Vertebral Osteomyelitis in Immunocompetent Hosts: Role of Triazole Antifungal Therapy. Clin Infect Dis. (2011) 52 (1): e1-e6.

11. Vinas FC, King PK, Diaz FG. Spinal aspergillus osteomyelitis. Clin Infect Dis. 1999;28:1223–9.

12. Walsh TJ, Anaissie EJ, Denning DW. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis2008;46:327- 360.

Assessment and Management of Attention-Deficit/Hyperactivity Disorder

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Attention-Deficit/Hyperactivity Disorder (ADHD) is one of the most commonly diagnosed psychiatric diagnoses in children and adolescents, affecting about 5% of children worldwide (1). Those un- or undertreated are at heightened risk for problems in school, work, relationships and overall functioning. Adults with ADHD are increasingly presenting to primary care physicians for assessment and management, as most adolescents with ADHD continue to have symptoms into adulthood (2). Pharmacological interventions for ADHD have been shown to be very effective, both in children and adults. An understanding of effective assessment and treatment, as well as potential adverse effects of pharmacological treatment, is important when these patients present in the primary care setting.

Proper assessment of ADHD relies on an integration of clinical information delivered from a variety of sources. This is particularly the case when assessing children and adolescents, as is an understanding of common comorbidities. ADHD is not typically diagnosed with neuropsychological testing alone, computerized assessments, labs, EEG or brain imaging. In children and adolescents, a review of rating scales and school records is a helpful approach. The website www.adhd.net is a good resource for free, downloadable ADHD rating scales, including the SNAP-IV and the Vanderbilt teacher/parent scales. Other helpful rating scales for purchase include the Conners, 3rd Edition teacher and parent rating scales, Brown ADD scales and the ADHD Rating Scale-IV. Broad-based rating scales, such as the Child Behavior Checklist (CBCL) can also be useful. In addition to teacher input, a review of school records, previous testing and Individual Aucation Plans (IEPs), if in place, can also be quite helpful.

After this review/assessment, a clinical interview is necessary for the diagnosis of ADHD. This should focus on the DSM-5 diagnostic criteria for inattentive and hyperactive/impulsive symptoms. Six or more criteria are required for the diagnosis in children and five or more for adults (see Figure 1). There are 3 subtypes based on the criteria met: inattentive type, hyperactive-impulsive type and combined type. In addition, there should be functional impairment in school, work or life situations, with symptoms present in 2 or more settings. Symptoms must be present before the age of 12 and not better explained by another disorder.

DSM-5 ADHD Diagnostic Criteria

Hyperactive-Impulsive Symptoms	Inattentive Symptoms
Frequently fidgets, taps hands/feet or squirms seated	Fails to notice details, makes careless errors
Frequently gets out of seat	Trouble maintaining attention
Runs and climbs when inappropriate	Appears not to listen even when spoken to directly
Unable to play quietly	Difficulty with organization
Frequently "on the go" as if "driven by a motor"	Trouble completing tasks or following through on instructions
Talks to excess	Loses or misplaces things
Blurts out answers before questions are answered	Avoids activities that require sustained attention
Trouble waiting turn or in line	Distracted by extraneous stimuli
Frequently interrupts or intrudes	Forgets easily

Figure 1

A medical assessment by a physician is also an important approach to assessment. In particular, a thorough cardiac assessment is necessary. Questions should include a history of cardiac defects, fainting or excessive shortness of breath during exercise, a first or second-degree relative with a myocardial infarction prior to the age of 30, a history of long QT syndrome or Wolf Parkinson White syndrome, and a history of murmurs or other cardiac anomalies.

In August 2008, the American Academy of Pediatrics and the American Heart Association published a joint statement on cardiovascular evaluation and monitoring in ADHD (3). Because certain heart conditions in children may be difficult or impossible to detect, they feel it is prudent to carefully assess children for heart conditions who need treatment for ADHD. They also

note that medications that treat ADHD have not been shown to cause heart conditions nor have they been demonstrated to increase the risk of sudden cardiac death. Their recommendation includes:

- Obtaining a patient and family health history and a physical exam focused on cardiovascular diseaserisk factors
- Acquiring an ECG is reasonable for a physician to consider. This should be at the physician's judgment and is not mandatory. Treatment for ADHD should not be withheld because an ECG is not done.
- Though some medications for ADHD may increase or decrease heart rate and blood pressure, this is usually not dangerous. However, vital signs should be monitored in children with certain heart condi tions as the physician feels necessary.

A multimodal approach to treatment planning should take place after the diagnosis of ADHD is made. This includes psychoeducation and patient, parent and school focused interventions. Good resources for families on the internet include the ADD Association (www.add.org), Children and Adults with ADD (www.chadd.org) and the American Academy of Child and Adolescent Psychiatry "Facts for Families" (www.aacap.org). Behavioral parent training and family or couples' therapy can also be helpful to address problems that occur with the diagnosis outside of the school setting. Educationally, school-focused interventions such as 504 plans, IEPs, behavioral classroom management and standardized testing accommodations can be useful. Patient-focused interventions typically involve pharmacotherapy, social-related interventions and general health maintenance.

Pharmacotherapy is the gold standard for treatment of ADHD. Amphetamine was first tested on pediatric headaches by Charles Bradley in the 1930s. Methylphenidate (MPH) was synthesized in 1944 and identified as a stimulant medication in 1954. Since that time, most medications for ADHD have been derived from these 2 stimulants. Given the length of time these medications have been in use, there is ample data to support their efficacy and safety, with data from over 300 controlled clinical studies (4). Stimulants are generally regarded as the most effective medications for ADHD with the most robust treatment effect size, and approximately 70% of patients respond favorably to the first stimulant prescribed (5, 6).

Stimulants work by influencing catecholamine activity in the prefrontal cortex (PFC) and enhance the ratios of preferred "signal" to nonpreferred "noise" pathways, which leads to improved attention and motor control. This can be achieved either by indirect effects of increased catecholamines or direct effects of alpha-2 agonists on glutaminergic signaling in the PFC (7). There are 2 classes of stimulant medications, methylphenidates (Ritalin, Focalin) and amphetamine salts (Adderall, Dexedrine). Both are equally effective with similar side effects in clinical studies, and finding the optimal medication is achieved through trial and error (2). There are many formulations of both medications, most of which involve length of action. The more commonly used extended release MPH formulations are MPH-ER OROS (Concerta) and dexmethylphenidate ER (d-MPH-ER; Focalin XR). Immediate release formulations of MPH and d-MPH are effective for about 4 hours, whereas MPH-ER and d-MPH ER can last 10-12 hours. Similarly, MAS-ER (Adderall XR) and lidexamfetamine (Vyvanse) can be effective for 10-12 hours, with IR MAS and dextroamphetamine lasting about 5 hours. There are many other formulations of mid- to long-acting stimulants, such as Ritalin-LA and Dexedrine Spansules, though the extended release medications mentioned above are the most commonly used in clinical practice and will therefore be the focus of this article (see Figure 2).

Extended-Release Stimulant Preparations

Stimulant	Dosages	Recommended Range
MPH-ER OROS (Concerta)	18, 27, 36, 54 mg	18-72 mg/daily
d-MPH ER (Focalin XR)	5, 10, 15, 20, 25, 30, 35, 40 mg	5-40 mg/daily
MAS-ER (Adderall XR)	5, 10, 15, 20, 25, 30 mg	5-30 mg/daily (5-60 mg/day in adults)
Lisdexamfetamine (Vyvanse)	20, 30, 40, 50, 60, 70 mg	20-70 mg /daily

Figure 2

There are also several non-stimulant medications approved for use in ADHD. Atomoxetine (Strattera) is a noradrenergic reuptake inhibitor FDA approved for ADHD. Intuniv (Guanfacine-ER) and Kapvay (Clonidine-ER) are 2 other approved medications that work through Alpha-2 receptor agonism (see Figure 3). While the immediate release formulations of guanfacine and clonidine are not FDA-approved for ADHD, these are often used in clinical practice.

Non-Stimulant Medications FDA-Approved for ADHD Treatment

Medication	Dosages	Recommended Range
Atomoxetine (Strattera)	10, 18, 25, 40, 60, 80, 100 mg	0.5-1.4 mg/kg daily (QD or BID)
Guanfacine ER (Intuniv)	1, 2, 3, 4 mg	1-4 mg/daily
Clonidine ER (Kapvay)	0.1, 0.2 mg	0.1-0.4 mg/day (QD or BID)

Figure 3

The choice of ADHD medication is generally provider-preferred, though several factors may be considered. Given the efficacy and safety of stimulant medications, these are generally considered to be first-line. MPH may be milder based on meta-analysis, and amphetamines may provide better coverage for adults (8). If a patient has a seizure disorder, MPH may be the preferred agent based on safety profiles (9). One practical consideration is whether or not the patient is able to swallow pills, as MPH-ER OROS cannot be crushed or chewed, while d-MPH ER, MAS ER and lisdexamfetamine are capsules that can be opened and placed in food. The various subtypes of ADHD respond similarly to all stimulant formulations and are generally not considered when starting an agent. Non-stimulant formulations are generally preferred if a patient cannot tolerate the adverse effects of stimulants, have a history of recent substance abuse or have concurrent anxiety.

Practitioners are often concerned about the risk of substance abuse and/or diversion in patients prescribed a stimulant. In systematic reviews of the relevant literature, there is no evidence that taking stimulants increases the risk for patients with ADHD to develop substance use disorders, and perhaps there may be reduced risk (10). In a case-controlled, longitudinal, prospective study, researchers found that patients with ADHD who were not treated had a 2.6 times higher risk to develop any SUDs at follow-up as compared to healthy controls and a 2 times higher risk than those with ADHD who did receive treatment (11). Should abuse be a concern, one choice may be lisdexamfetamine. Lisdexamfetamine itself is inactive prior to its absorption, and the subsequent rate-limited enzymatic cleavage of the molecule's L-lysine portion produces the active metabolite (dextroamphetamine). Choosing a non-stimulant medication for ADHD is another option if there are concerns about abuse potential.

Once a stimulant is chosen to prescribe, it is best practice to try several doses of the medication over the period of 2-3 weeks to identify optimal dosing, as the medications are effective immediately after initiation, and adverse effects such as discomfort, headache and nausea typically subside after several days. In the state of California, prescriptions are valid for 6 months after the date written, allowing some leeway in how to best achieve this (though this rule is state-dependent). It is possible to prescribe a stimulant whereby the patient is able to try 3 different doses over the period of 15 days, with a 30-pill/capsule supply. A prescription should be written with the chosen agent and lowest starting dose with instructions stating "Take 1-3 by mouth daily as directed." The total daily dosed should be given first thing in the morning. Then, a more detailed patient instruction sheet is given to the patient, as detailed in Figure 3.

Medication/Dose	# Dispensed	Patient Instructions
MPH-ER OROS 18 mg	#30, 1-3 PO QAM AD	1 tab for 5 days, 2 tabs for 5 days, 3 tabs for 5 days
d-MPH ER 5mg (<25 kg) d-MPH ER 10 mg (>25 kg)	#30, 1-3 PO QAM AD	1 cap for 5 days, 2 caps for 5 days, 3 caps for 5 days
MAS-ER 5 or 10 mg (depending on age)	#30, 1-3 PO QAM AD	1 cap for 5 days, 2 caps for 5 days, 3 caps for 5 days
Lisdexamfetamine	#30, 1-3 PO QAM AD	1 cap for 5 days, 2 caps for 5 days, 3 caps for 5 days

Figure 3

Following these guidelines allows the clinician and patient to try 3 different dosages of the prescribed medication and then follow up in 2-3 weeks to discuss the experience. Once a preferred dose is identified, a prescription for one month can be written for a longer trial. If this trial is successful, 90 days of medication can be dispensed, with the patient returning to the provider every 3 months, as dictated by FDA rules for Schedule II prescribing. This can be done in 2 ways. Most insurance companies allow for 90-day prescriptions, including for Schedule II stimulants. Another method which is allowable by the California state and DEA rules mentioned above involves prescribing the patient 3 separate prescriptions for 30 day supplies. These prescriptions should all be dated the date of the visit, as post-dating prescriptions is not allowed. On the second prescription, one should write, "Do not fill (DNF is acceptable) before (30 days after the date written), and the other "DNF before (60 days after the date written). This allows for better control of the medication prescribed and prevents the patient from filling all 3 prescriptions at once.

Common side effects of stimulants include appetite loss, insomnia, nausea, abdominal pain, headache, dizziness, dry mouth and dysphoria. Height deceleration is a documented adverse effect. This can be mediated by lowering the stimulant dose, as appetite loss is dose-de-

pendent. Increased irritability or rebound hyperactivity can also be seen when the medication is wearing off in the afternoon. Should the patient fail the first stimulant trialed, either because of ineffectiveness or intolerable adverse effects, another stimulant, usually from the other class, should be tried. All attempts to find an effective, tolerated stimulant should be made, given the efficacy of this class. Either switching to a non-stimulant medication or the use of these in combination therapy is an option. Should gastrointestinal complaints persist, there is Daytrana, a MPH patch that bypasses the GI system. If side effects are present at higher doses of stimulants, the dose can be decreased with the addition of an alpha-agonist or atomoxetine as augmentation.

If the length of action of the stimulant is insufficient, an immediate-release (IR) formulation of the extended release (ER) medication prescribed may be added in the afternoon, always remaining within the same class of stimulant. MPH and MAS are generally used in their respective classes. When considering the dose of an IR preparation, it is important to add a dose equivalent to or higher than the individual doses released in the ER preparations. MAS-ER, lisdexamfetamine and d-MPH ER OROS are medications that release in a biphasic manner. Thus, an IR dose of at least half the dose of the ER preparation should be added. For instance, an afternoon dose of 10 mg MAS IR should be added to a morning dose of MAS-ER 20 mg. MPH-ER OROS is released triphasically, and the dose should approximate the ER dose divided by 3. Therefore, a morning dose of 36 mg MPH-ER OROS should be augmented with 10 mg MPH in the afternoon.

One question that often arises from patients and parents is how long they will need to be on the medication. Long-term maintenance with a stimulant is often needed by the patient, as most patients diagnosed with ADHD as children continue to exhibit symptoms into adulthood. Recommendations for long-term maintenance include assessment of height/weight, pulse and BP every 6 months. Trial periods off the medication can be useful to assess continued need. One nice feature of stimulants is that they can be held on weekends or holidays to assess this, or if appetite is compromised and there is concern about food intake and its effect on growth.

Parents and patients often inquire about alternative therapies for ADHD. Omega-3 fatty acid supplementation does have evidence to support its benefit in ADHD (12). Restriction/elimination diets, other supplements and caffeine do not have evidence to support their use. There is also preliminary evidence to support repetitive trigeminal nerve stimulation (TNS) as an effective alternative for ADHD treatment (13).

Patients with ADHD are presenting more frequently to primary care providers, and an understanding of the assessment and treatment is necessary to appropriately provide adequate care. A more detailed breakdown of the various stimulants available can be helpful, though a basic understanding of the preferred agents used is likely most helpful for primary care physicians. In difficult cases, referral to a child and adolescent psychiatrist for evaluation may be prudent.

References

1. Abramowicz M. Treatment guidelines from the Medical Letter. The Medical Letter. 2011;9: 23-8.

2. McGough JJ. ADHD. Oxford American Psychiatry Library. 2014.

3. Perrin JM, Friedman RA, Knilans TK, the Black Box Working Group, the section on cardiology and cardiac surgery. Cardiovascular monitoring and stimulant drugs for attention-deficit/hyperactivity disorder. Pediatrics. 2008:122(2):451-3.

4. Biederman J, Spencer TJ. Psychopharmacological intervention. Child Adolesc Psychiatr Clin N Am. 2008;17:439-58

5. Wigal SB. Efficacy and safety limitations of attention-deficit-hyper activity disorder pharmacotherapy in children and adults. CNS Drugs. 2009;23:21-31.

6. Elia J, Borcherding BG, Rapoport JL, Keysor CS. Methylphenidate and dextroamphetamine treatment of hyperactivity: are there true nonresponders? Psychiatry Res. 1991;36:141-5.

7. Arnsten AF, Rubia K. Neurobiological circuits regulating attention, cognitive control, motivation, and emotion: disruptions in neurode velopmental disorders. J Am Acad Child Adolesc Psychiatry. 2012;51:356-7.

8. Faraone SV, Buitelaar J. Comparing the efficacy of stimulants for ADHD in children and adolescents using met-analysis. Eur Child Adolesc Psychiatry. 2010;19:353-64.

9. Fosi T, Lax-Pericall MT, Scott RC, Neville BG, Aylett SE. Methyl phenidate treatment of ADHD in young people with learning disability and difficult to treat epilepsy: evidence of clinical benefit. Epilepsia. 2013;54:2071-81.

10. Wilens TE, Faraone SV, Biederman J, Gunawardene S. Does stimulant therapy of attention-deficit/hyperactivity disorder beget later substance abuse? A meta-analytic review of the literature. Pediatrics. 2003;111:179-85 .

11. Schneider BN, Enenbach M. Managing the risks of ADHD treatments. Curr Psychiatry Rep. 2014;16(10):479.

12. Bloch MH, Qawasmi A. Omega-3 fatty acid supplementation for the treatment of children with attention-deficit/hyperactivity disorder symptomatology: systematic review and meta-analysis. J Am Acad Child Adolesc Psychiatry. 2011;50:969-71.

13. McGough JJ, Loo SK, Sturm A, Cowen J, Leuchter AF, Cook IA. An eight-week, open trial, pilot feasibility study of trigeminal nerve stimulation in youth with attention-deficit/hyperactivity disorder. Brain Stimul. 2015:8(2):299-304.

The Importance of a One Health Perspective in a Changing Environment

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Introduction

One Health recognizes that the health of people is connected to the health of animals and the environment — Centers for Disease Control and Prevention (CDC) (1)

The One Health view leads the scientific community to consider the interconnectedness of humans, animals and the environment rather than studying them in isolation. This, advocates believe, can lead to improvements in understanding, preventing and treating human and animal diseases. There is nothing new here; we have always understood that the three are connected, that their Venn diagrams intersect.

However, rapidly changing global conditions have brought about a spike in attention to the One Health framework. What conditions specifically? There is an increase in human migration brought about by politics, sectarian aggression, improved transportation systems and, most notably, climate change. Warming of the planet has affected human and animal migration patterns — and not just large land and sea animals but small vectors as well — and these have had a particularly noticeable impact on human health. The mosquito, for instance, which we'll discuss in a moment, has had a field day venturing into regions once known to be inhospitable to these temperature-sensitive insects. The climate impacts insect vectors, which, in turn, impact animal and human health.

The point is that a constellation of conditions has altered how humans and animals interact, where they interact and the health implications of their encounters. We will look at several examples later in this article.

More than an academic exercise, this framework for understanding the complex interrelationships is valuable for clinicians. Their expectations for the surfacing of a disease and their diagnoses and treatments of patients can benefit from an understanding of a broad range of contributing factors, especially in a time of accelerating changes.

Consider this example: Warming temperatures hasten the movement of plants and animals to regions where earlier

they could not have survived. The Aedes aegypti mosquito has been found in large numbers in sections of North America where it was never before seen. Consequently, diseases borne by Aedes aegypti are spread to humans and animals in areas where the diseases previously were rarely a concern. Fortunately, the spread of Zika never reached the levels predicted by some researchers in the early days of the disease outbreak, but Zika did attain a geographic spread we would not have expected only a decade or two earlier when the climate was more hostile to the vector.

Consider another factor: Not only does a warming climate enable the mosquito to venture into new territory, but viruses grow more quickly in warmer temperatures, which allow the virus to develop more rapidly within the mosquito's body. That's a critical point when you consider the relatively short lifespan of a mosquito — about 10 to 12 days. According to Tom Scott, a professor of entomology and epidemiology at the University of California, Davis, that's also about how long, on average, it takes for a virus to grow. So ordinarily most mosquitos have only a brief day or two to spread the disease. When the virus within the mosquito grows more rapidly, however, it arms the mosquito for more of its life to infect people before it dies (2). This is no small matter when so many viruses are spread by the mosquito, which now has more days to spread an infection across a wider geographic region. This example lays bare the interconnectedness of animals, humans and the environment.

In this brief introductory article, we look at the implications of considering the intersection of human and animal health and conditions of the environment. WiRED International, a non-profit organization that provides global health education in underserved regions, is configuring its training programs to reflect the principles of One Health. There is often more human-animal contact in places WiRED works than in most Western countries. Moreover, the impact of climate change can be even greater. Food-growing areas have dried up, forcing entire populations to move; sea level rise has driven people back from the sea; vectors have become more aggressive because of warmer temperatures and increased rainfall; and people in under-served regions often don't have the resources to fend off mosquitos, ticks, chiggers and other carriers. There is every reason to believe that these threatening conditions will continue and expand into the future, and so the importance of a One Health framework offers a critical structure for the understanding of human and animal health, now to be reflected in WiRED's training material.

Western University of Health Sciences, where two of the authors of this article are professors, is launching programs that include the study of One Health for its medical and veterinary students. Yes, the concepts of One Health, around for more than a hundred years, have become more prominent during the past two decades because of the benefits evident in such an integrated view of health. Physicians and veterinarians of tomorrow — faced with the overwhelming forces in play by a changing environment and rapidly shifting patterns of human and animal migration — must embrace a wide view that includes in a single frame the understanding of the three key elements interrelated in their effects on the planet and its inhabitants.

Background history

As we stated, it has been known since the 19th century that human health and animal health are interdependent and both connected to the health of their common ecosystems. The names most associated with this thinking are Rudolf Virchow, M.D. (1821–1902), and William Osler M.D. (1849–1919), both of whom are credited with the recognition of a link between human and animal health. Prominence of this view has ebbed and flowed over the years, and resurfaced in 1964 at the University of California, Davis. It became even more pronounced in 2000, when the One Health tag was introduced as a "holistic approach" to prevent epidemic/epizootic diseases and to maintain ecosystem integrity.

The One Health concept became an approach "to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes" (3). CDC refers to One Health as "a collaborative, multisectoral, and trans-disciplinary approach — working at the local, regional, national, and global levels — with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment" (underline ours) (1).

The common theme among all definitions of One Health is the tight relationship among humans, animals and the environment and, accordingly, the logic of rigorous collaborations across sectors. Fundamental to such working relationships is the recognition of direct impacts on health by working across silos and optimizing resources while respecting the autonomy of the participating sectors.

The One Health approach has been formally recognized by all major health agencies, including the U.S. Department of Agriculture, CDC, the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations, the European Commission and

many others.

What is the logic of One Health thinking?

One Health has gained prominence because of a measured emergence and re-emergence of many infectious diseases affecting humans and animals worldwide. At the heart of One Health thinking are causal factors such as rapid population growth, globalization of human activity and environmental changes. These factors change the dynamics of interactions among people and among people and animals and the conditions that bring about or exaggerate changes in the spread of disease. Previously, we discussed the simple example of how climate change has increased the capacity of mosquitos to spread infections more quickly and more widely. That is one of many instances where disease today can be spread at an accelerated pace.

Consider the emergence of a number of zoonotic diseases — including HIV, Ebola, Rift Valley Fever, Lyme disease, West Nile virus and many more — that have imposed worldwide risks to public health. As we noted, these risks increase with globalization, climate change and changes in human behavior, giving pathogens numerous opportunities to colonize new territories and to evolve into new forms. The most evident example in this group is Ebola, where simply touching an infected individual or the belongings of an infected individual may be enough exposure to transmit the virus. Migration has obvious implications for such a virulent disease.

Population migration patterns impact the spread of disease, and we are seeing more evidence that climate change may be a great accelerator. A warming planet endangers health by affecting water resources, agriculture, infrastructure and ecosystems. Additionally, the prevalence of infectious diseases transmitted through food, water and insects is influenced significantly by climate factors, primarily high and low temperature extremes and precipitation patterns.

Vector-borne diseases are among the most complex of all infectious disease. WHO estimates vectors to account for more than 17% of all infectious diseases (4). Further, WHO estimates that every year there are more than 1 billion cases globally and more than 1 million deaths from vector-borne diseases, such as malaria, dengue, schistosomiasis, Chagas disease and yellow fever. In the United States, the U.S. Global Change Research Program reported 14 vector-borne diseases that are currently of national public health concern (5). These diseases are difficult to prevent (vaccines are available for only a few vector-borne diseases) and control in part because the vectors themselves integrate so thoroughly within the human and animal populations.

Implications of climate change and vector control

With respect to environmental impact on vector populations, the current debate on climate change around the world and especially in the United States takes on a new urgency. Despite overwhelming evidence from thousands of studies, remarkably there is a small but influential group that argues climate change is a fiction. Their resistance to the data is more than a curiosity when it translates into policies that directly impact human and animal health. Curbing the use of fossil fuels can slow the changes already underway, but unaltered, continued burning of carbon-based fuels will lead to exaggerated environmental conditions with dangerous consequences. One of them is to increase the deadly impact of disease-bearing vectors.

Zoonotic diseases

We have discussed vector borne diseases, but zoonotic diseases, infections shared between humans and animals, are a key feature of One Health discussions. Zoonotic diseases can be caused by the range of infections, including bacteria, viruses, parasites and fungi. Moreover, zoonotic diseases are more common than many people think. CDC reports that more than 60% of infectious diseases in humans are spread from animals and that 75% of new or emerging infectious diseases are spread from animals (6).

How are the infections spread? In four ways:

Direct contact. Humans can be infected by coming in contact with body fluids from an infected animal. Being bitten or scratched and even touching an animal can transmit the infection.

Indirect contact. Environments in which animals have lived or roamed may harbor the infectious agents that can be picked up by humans. Barnyards and watering troughs are common areas for indirect contact.

Vector-borne. We have discussed vectors earlier. Insects such as mosquitos and ticks are considered to be animals for this discussion, and as we have seen, their bites and stings can transmit infection.

Foodborne. The feces of infected animals can be found on fruits and vegetables that have not been properly washed. Undercooked meat or eggs and unpasteurized milk can also become a source of infections. CDC reports that fully 1 in 6 Americans each year become sick from eating contaminated food.

It has long been known that animals can transmit disease to humans, so nothing is new here. But, how does this fact fit into our discussion of One Health? While

animal-human transmission has occurred for thousands of years, new migration patterns — caused by factors we noted earlier, including political turmoil, climate change influences on food resources and sea level rise — elevate the concern for rapidly changing patterns of human to human and human to animal contact.

Plants once unable to survive in the cool temperatures associated with higher elevations and higher latitudes now move into these areas that have warmed from climate change, and the animal populations that live in these habitats move as well, putting animals in contact with humans to whom they have not been previously exposed. Diseases travel and spread with their animal hosts and introduce humans to new profiles of infectious diseases (7). The dynamics are complex and involve the interplay of human institutions and human-animal contact, climate change, food supplies and shifts in available land where humans can survive.

Yes, there has always been human and animal migration; what is new is the speed with which it is occurring today (8). The movement of populations is faster. Droughts, floods, extreme temperatures, wild fires and other environmental conditions are accelerating and, accordingly, the migrations of humans, animals and plants are occurring at a faster pace. These rapid changes make the framework of One Health thinking ever more important in our understanding of the influences on human health. While the bottom line concern of physicians is the health of human beings, it is becoming ever more evident that we cannot think about human health in isolation. That was never a wise construction and it is even more untenable today at a time when the influences on human health are more complex, more evident and happening ever more rapidly.

Healthcare professional roles in One Health

Communication and collaboration among healthcare professionals — along with their national and international affiliates and their alliance with the United Nations and nongovernmental organizations — play a significant role in the advancement of One Health. This is so because collective action is more effective than individual group action; collective advocacy draws greater public awareness of the interrelationships among human, animal and environmental health.

Such alliances naturally take us beyond the conventional settings of healthcare professionals — hospitals and clinics, medical and veterinary schools, research labs. A natural follow-on to One Health thinking is that an evolving role of medical and veterinary professionals is to inform the debate. No one can speak with greater authority than these experts who recognize the One Health construction, who know the science and recognize the constellation of forces acting on human and animal health. At the end of the day, it may fall to medical and veterinary practitioners, who see health impacts on the ground, to be certain the One Health view is represented in critical policy discussions at the local, regional and global levels.

References

1. CDC.gov. One Health. https://www.cdc.gov/onehealth/basics/history/index.html, accessed 10/15/2017.

2. Associated Press. Higher Temperatures Make Zika Mosquito Spread Disease More. 2016. https://weather.com/science/news/warm-temperatures-allow-zi-ka-spreading, accessed 10/15/17.

3. WHO.org. One Health. http://www.who.int/features/qa/one-health/en/, accessed 10/15/2017.

4. WHO.org. Vector-borne Diseases. http://www.who.int/mediacetre/factsheets/fs387/en/, accessed 10/15/2017.

5. U.S. Global Change Research Program. https://health2016.globalchange.gov/, accessed 10/15/2017.

6. CDC.gov. Animal-Human Diseases (Zoonoses). https://www.cdc.gov/globalhealth/countries/nigeria/what/zoo.htm, accessed 10/15/17.

7. Thomas T. Moore. Climate change and Animal Migration. JSTOR, 41:2, Spring 2011, pp. 393-405. http://www.jstor.org/stable/j43267496?seq=1#page_s_ can_tab_contents, accessed 10/15/17.

8. Frank Seebacher and Eric Post. Climate Change Impacts on Animal Migration. Climate Change Responses, 2015, 2:5. https://doi.org/10.1186/s40665-015-0013-9, accessed 10/15/17.

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Moyamoya Disease:
A chronic headache in the primary

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Case Report

Patient is a 53-year–old male who started experiencing headaches in the 1990s. He was hospitalized for a CVA with right hemiparesis in October 2011. A CT head w/o contrast was normal compared to his previous imaging in 2010. An MRI brain w/o contrast showed white matter small-vessel chronic ischemia without evidence of acute brain injury. Carotid ultrasound was unremarkable. Years passed and patient visited a pain management specialist in 2014 and received injections for pain. From August 2015 to October 2016, patient received physical therapy for cervical myofascial pain, headaches, and cervical degenerative joint disease. In May of 2014, an inspiration and expiration chest x-ray with independent fluoroscopy showed elevated right hemidiaphragm. A CT neck with contrast on 6/5/14 was unremarkable, while a CT scan of thorax with contrast revealed significantly elevated right hemidiaphragm that may be related to phrenic nerve paralysis/injury. In February of 2016, CT angiogram of the head and neck revealed left M2 segment blockage. In December of 2016, a cerebral angiogram showed occlusion of Left MCA with neovascularization. Moyamoya syndrome was diagnosed as stage IV to V. Pitfalls in the management of this patient highlight the importance of proper chronic headache management in the primary care setting.

Moyamoya Disease

Background:
Moyamoya disease (MMD) is a cerebral vascular disease in which there is bilateral stenosis or occlusion of the terminal portion of the internal carotid arteries, and/or proximal anterior cerebral artery artery and middle cerebral artery, along with formation of arterial collateral circulation. This disease is termed "moyamoya", a Japanese phrase meaning "puff of smoke", which is used to describe the abnormal appearance of the vascular collateral circulation on angiography (1). The three blood vessel layers are the intima (innermost layer), media (muscular layer), and adventitia (outermost layer). In MMD, a histopathological study indicated eccentric fibrous intimal thickening with laminated elastic fibers, collapse of the lumen, and fibrosis in 14 out of 22 subjects. The moyamoya collateral vessels were found to consist of dilated medium or small-sized arteries that branched off the circle of willis, and identical to lenticu-

lostriate and thalamoperforate arteries (2).

Although the etiology of MMD is not fully understood, genetic studies have identified the RNF213 gene on chromosome 17q25.3 as an important susceptibility marker for MMD in East Asian populations (3). A study of familial MMD indicate an autosomal dominant mode of inheritance with incomplete penetrance (4). A study from Japan demonstrated that the c.14576G>A variant in the RNF213 gene was identified in 95.1% of patients with familial MMD, and 79.2% of patients with sporadic MMD (5). This genetic marker may be a beneficial tool for identifying patients with early-onset and severe form of MMD.

Epidemiology

MMD has been found to be relatively common in East Asian countries compared to countries in the Western hemisphere. A 1995 hospital survey in Japan reported a prevalence of MMD as 3.16/100,000 and incidence of 0.35/100,000 (6). A 2003 study in Japan demonstrated a higher prevalence of MMD in women, with sex ratio of women-men of 1.8:1 (7). An epidemiological study of MMD in California and Washington state showed an incidence of 0.086/100,000 persons during a period of 1987 to 1998, which is lower than reported in Japan (8).

Presentation

Clinical presentations associated with MMD include headache, seizure, cognitive impairment, hemorrhagic stroke, ischemic stroke, and TIA (9). The initial clinical presentation of MMD has been shown to be variable in different regions and age groups. In a 2012 systematic review, intracerebral hemorrhage was found to be an initial presentation in 56% in China, 52% in Taiwan, 29% in Hawaii, 21% in Japan, and 10% in Iowa. In all regions, ischemia was found to be an initial clinical presentation in >75% of individuals with a childhood onset (10).

Migraine-like headaches are a common symptom of MMD and may be due to stimulation of dural nociceptors by dilated transdural collaterals, or a symptom of chronic hypoxemia (11).
Moyamoya disease is classified based on angiographic progressions developed by Suzuki and colleagues into six stages (12):

Stage 1 - Narrowing of Carotid fork. Only the carotid fork stenosis is observed.
Stage 2 - Initiation of basal moyamoya. All the main cerebral arteries are dilated.
Stage 3 - Intensification of moyamoya. Remarkable moyamoya vessels at the base of the brain. The defection of the middle and anterior cerebral arteries is observed.
Stage 4 - Minimization of moyamoya. The defection of the posterior cerebral artery is observed.
Stage 5 - Reduction of moyamoya. All the main cerebral arteries are missing.
Stage 6 - Disappearance of moyamoya. Cerebral blood supplied only from external carotid arteries.

Diagnostic Work-Up

Laboratory and imaging studies are both contributory to the diagnosis of MMD. In stroke patients with indeterminate etiology, indicated labs include Protein C, Protein S, Antithrombin III, Homocysteine, and Factor V Leiden. These identify a hypercoagulable state as a cause. Studies have shown that there is an association between elevated thyroid function and thyroid autoantibodies and MMD, especially in pediatric patients (13). Accordingly, monitoring thyroid function is also indicated.

Neuroimaging, including head CT, brain MRI, transcranial Doppler ultrasonography, and angiography, is essential to the diagnostic workup of this disease. On CT scan, findings of infarction can be seen in both cortical and subcortial regions. Different stages of the disease have distinct CT presentations. A retrospective study of 32 adults with MMD presenting with first time ischemic stroke showed that patients with early stage MMD (Suzuki stage 1 or 2) had ischemia in deep subcortical areas, whereas those with later stages (Suzuki stage 3 or higher) had cortical lesions (14). Incidence of hemorrhagic stroke in subcortical and cortical regions are much less reported. Hemorrhage is predominantly found in the basal ganglia, thalamus, and/or ventricular system. Brain MRI is the preferred imaging modality, specifically diffusion and perfusion MR studies, for small or acute ischemic events. Multiple punctate flow voids seen on MRI are diagnostic of moyamoya, which are manifestations of dilated collateral vessels in the basal ganglia and thalamus. Increased signal in the leptomeninges and perivascular spaces on post contrast T1 and fluid- attenuated inversion recovery (FLAIR) images is known as "the ivy sign," which is suggestive of decreased cerebrovascular reserve (15). Transcranial Doppler ultrasound (TCD) is a noninvasive method of assessing hemodynamics by measuring blood flow velocity, which shares an inverse relationship with arterial diameter. Doppler is used for initial diagnosis, as well as progression of the disease with the use of TCD serial studies. Conventional angiography is the gold standard for diagnosing, which shows stenosis or occlusion of the internal carotid distally and bilateral anterior cerebral and middle cerebral arteries proximally. This medium of diagnostic imaging also demonstrates the neovascularization at the basal ganglia.

Discussion

MMD is an idiopathic, progressive stenosis or occlusion of the distal internal carotid arteries that leads to neovascularization and a network of collaterals. Initially, moyamoya showed a heavy predominance in the Asian population, but is now being seen in broader demographics. It is rarely observed in African Americans. The peak of incidence is bimodal, presenting in 5-year-old children and adults in their mid 40's (16).

MMD presents with recurrent migraine like headaches that is refractory to medical treatment. Though the mechanism remains unclear, it is known to be multifactorial. Headache associated with the disease is a materialization of blood vessel pathology. Studies show that cerebral artery nociceptors induce nausea and referred pain in areas involved in migraine attacks with stretching of intracerebral vessels (17). Other manifestations include cerebral aneurysms and arteriovenous malformations which may account for headaches by two potential mechanisms. Trigeminal nociceptors are stimulated by stretching of the growing aneurysm. The alternate mechanism involves an aneurysmal bleed into the subarachnoid space, which has a clinical presentation of a pulsatile headache and associated photophobia, nausea, and vomiting.

MMD involves a neurogenic inflammatory process that can produce headaches. Similar to the mentioned mechanisms, the inflammation causes stretch of intracranial perivascular nociceptors which leads to release of substance P and calcitonin gene-related peptide from the trigeminal nerve endings. The generated headache is sustained by further activation of nociceptor by the released pro-nociceptive mediators (18). This disease also produces an intracranial hypovolemic state due to the reduced blood flow to the brain. The hypoperfusion and hypoxemia is also a likely etiology of headache.

A study revealed that 38% of 651 patients with MMD initially treated medically continued to have progressive symptoms and eventually required surgical management (19). Medical treatment includes use of antiplatelet therapy and calcium channel blockers. Calcium channel blockers have shown some efficacy in reducing headaches and incidence of TIAs in moyamoya patients. This class of medication is used with caution, as it can cause hypotension, which can exacerbate symptoms. Surgical intervention is the preferred and superior treatment. There are two methods of revascularization: direct and indirect. Direct vascularization is direct anastomosis of a branch of the external carotid artery to a cortical artery. Indirect vascularization leads to neovascularization in the cerebral cortex by placing vascularized tissue supplied by the external carotid artery in direct contact with the brain.

MMD is known to be a rare disease with uncertain etiology, but headache is one of the most common presentations in a primary care setting. Headaches and migraines may be the first presenting symptom of this disease. This finding is not diagnostic. Moyamoya should be considered a differential in new onset, refractory migraine-like headache, with or without associated neurological symptoms. Neurovascular imaging as part of the diagnostic workup for headache or migraine can increase identification of early stage moyamoya and prevent further progression with proper and prompt management. By broadening the differential of patients reporting headache and taking appropriate diagnostic measures, there can be significant reduction of stroke occurrence and resulting neurological deficits caused by this rare disease.

References:

1.Suzuki J, Takaku A. Cerebrovascular "moyamoya" disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol. 1969;20(3):288-99.

2.Yamashita M, Oka K, Tanaka K. Histopathology of the brain v ascular network in moyamoya disease. Stroke. 1983;14(1):50-8.

3.Fujimura M, Bang OY, Kim JS. Moyamoya Disease. Front Neurol Neurosci. 2016;40:204-220.

4.Mineharu Y, Takenaka K, Yamakawa H, et al. Inheritance pattern of familial moyamoya disease: autosomal dominant mode and genomic imprinting. J Neurol Neurosurg Psychiatr. 2006;77(9):1025-9.

5.Miyatake S, Miyake N, Touho H, et al. Homozygous c.14576G>A variant of RNF213 predicts early-onset and severe form of moyamoya disease. Neurology. 2012;78(11):803-10.

6.Wakai K, Tamakoshi A, Ikezaki K, et al. Epidemiological features of moyamoya disease in Japan: findings from a nationwide survey. Clin Neurol Neurosurg. 1997;99 Suppl 2:S1-5.

7.Kuriyama S, Kusaka Y, Fujimura M, et al. Prevalence and clinicoepi demiological features of moyamoya disease in Japan: findings from a nationwide epidemio logical survey. Stroke. 2008;39(1):42-7.

8.Uchino K, Johnston SC, Becker KJ, Tirschwell DL. Moyamoya disease in Washington State and California. Neurology. 2005;65(6):956-8.

9.Kim JS. Moyamoya Disease: Epidemiology, Clinical Features, and Diagnosis. J Stroke. 2016;18(1):2-11.

10.Kleinloog R, Regli L, Rinkel GJ, Klijn CJ. Regional differences in incidence and patient characteristics of moyamoya disease: a systematic review. J Neurol Neurosurg Psychiatr. 2012;83(5):531-6.

11.Guey S, Tournier-lasserve E, Hervé D, Kossorotoff M. Moyamoya disease and syndromes: from genetics to clinical management. Appl Clin Genet. 2015;8:49-68.

12.Suzuki J, Kodama N. Moyamoya disease--a review. Stroke. 1983;14(1):104-9.

13. Li H, Zhang ZS, Dong ZS, et al. Increased Thyroid Function and Elevated Thyroid Autoantibodies in Pediatric Patients with Moyamoya Disease: A Case- Control Study. Stroke. 2011 February 24.

14. Kim JM, Lee SH, Roh JK. Changing ischaemic lesion patterns in adult moyamoya disease. J Neurol Neurosurg Psychiatry 2009; 80:36.

15. Mori N, Mugikura S, Higano S, et al. The leptomeningeal "ivy sign" on fluid-attenuated inversion recovery MR imaging in Moyamoya disease: a sign of decreased cerebral vascular reserve? AJNR Am J Neuroradiol 2009; 30:930.

16. Baba T, Houkin K, Kuroda S: Novel epidemiological features of moyamoya disease. J Neurol Neurosurg Psychiatry. 2008; 79(8): 900–4.

17. Olesen J, Burstein R, Ashina M, Tfelt-Hansen P (2009) Origin of pain in migraine: evidence for peripheral sensitization. Lancet Neurol 8:679-690.

18. Panconesi A, Bartolozzi ML, Guidi L (2009) Migraine pain: reflections against vasodilation. J Headache Pain 10(5):317-325.

19. Scott RM, Smith ER (2009) Moyamoya disease and moyamoya syndrome. N Engl J Med 360(12): 37-1226.

Brain Repair After Stroke

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Stroke therapies

Disability after stroke remains a major clinical concern. In middle- and high-income countries, stroke is the leading neurological cause of lost disability-adjusted life years 1. An estimated 6,600,000 Americans adults have had a symptomatic stroke, and 13,000,000 people in the US have had a silent stroke [2]. Each year, 795,000 people experience a stroke, of which 610,000 are first-ever symptomatic stroke. The mean survival after stroke is 6-7 years, with approximately 85% of patients living past the first year of stroke [3].

Current therapies for acute stroke are accessed by a limited fraction of patients and furthermore reduce disability in only a subset of patients. A limited fraction of patients receives IV tPA acutely after stroke [4,5,] in large part due to the narrow time window for safe drug administration; according to recent estimates, approximately 5% of stroke patients receive this medication 5. Moreover, of those so treated, half or more have significant long-term disability [6,7]. Even fewer patients receive acute endovascular reperfusion therapies 8. Brain repair treatments generally have a time window measured in days-months and so have the potential to help a large proportion of patients affected by stroke.

Brain repair can be defined as restoring CNS structure or function after an injury such as stroke. This repair can be spontaneous or therapeutically induced. Brain repair differs from prevention or acute treatment strategies. Neural repair is focused on regrowth, restoration, rewiring, and rehabilitation.

Spontaneous Recovery from Stroke

Brain events following a stroke can be organized into three recovery epochs. The first represents acute injury during the initial hours after stroke. The second commences days to weeks following stroke and corresponds to neural repair. Mechanisms of spontaneous recovery are most robust during this time [9]. The third is a chronic phase of neural repair whereby the brain is relatively stable but modifications in brain structure and function are still possible with specific treatments.

Treatments to Promote Neural Repair

Many types of restorative therapy to incite neural repair are under study [10-13]. Most are in early phase clinical trials.

Growth factors play a critical role in spontaneous neural repair through mechanisms that include angiogenesis, reduced apoptosis, stem cell proliferation, and immunomodulation [14]. In some cases, a rich clinical experience exists for growth factors outside of stroke indications, such as for patients with renal failure or infertility. Most human stroke studies to date have examined hematopoetic growth factors, some of which have an extensive record of safe application in humans. Granulocyte-colony stimulating factor (G-CSF) is one such growth factor. The AXIS-2 study [15], compared G-CSF with placebo in 328 patients < 9 hours post-stroke using a multicenter, randomized, placebo-controlled design. G-CSF was not different from placebo 90.

One preclinical study suggests that systemically administered erythropoietin may enter the brain and improve outcome when introduced with a delay such as 24 hours post-stroke [16]. Other studies found favorable effects of sequential growth factor administration, giving epidermal growth factor [17] or beta-human chorionic gonadotropin (hCG) [18] followed by erythropoietin, beginning 1-7 days after stroke, possibly by increasing neural stem cell levels. This approach was directly translated to humans in the beta-hCG+erythropoietin in acute stroke (BETAS) study, a single-dose, multisite, open-label, non-controlled safety trial that gave 3 hCG doses beginning 1-2 days post-stroke followed by 3 erythropoietin doses beginning 7-8 days after stroke. No safety concerns were identified [19.] The safety of erythropoietin was also found in a randomized placebo-controlled study of 167 patients who

received two doses of erythropoietin vs. placebo beginning 48 post-stroke [20]. The BETAS study was followed by the REGENESIS study [21]. This was intended to be a randomized, placebo-controlled, double-blind proof of concept study of sequential hCG and erythropoietin using the BETAS study treatment schedule. This trial was put on hold by regulatory authorities due to concerns related to an acute stroke neuroprotective trial [22] that initiated erythropoietin <6 hours of stroke onset, even though the REGENESIS trial initiated erythropoietin 7-8 days post-stroke. Subsequently, the REGENESIS trial was modified to be a dose-ranging safety study and, due to financial constraints, largely moved to India. Enrollment was terminated by the sponsor early after 96 enrollees. Treatment groups did not differ in safety or in the primary endpoint, NIHSS score change to Day 90.

The post-stroke restorative effect of other large molecules, such as monoclonal antibodies, is also under study. A monoclonal antibody modulates activity within a targeted signaling pathway by binding to a specific target such as a receptor or cell surface marker. One approach in this context focuses on neutralizing factors that inhibit growth in the adult CNS, with the overall model being that neural repair after stroke after CNS injury is limited by the lack of a permissive growth environment. Axonal growth has long been known to occur in the peripheral nervous system [23]; however, in the CNS three major inhibitors (myelin-associated glycoprotein [MAG], oligo-myelin glycoprotein, and Nogo-A) result in the lack of a permissive growth environment. Furthermore, levels of these molecules increase after stroke [24,25]. Blockade of these inhibitors, such as with a monoclonal antibody, promotes axonal growth [26,27]. A monoclonal antibody can be used to neutralize these inhibitory CNS signals and promote axon growth after injury. A recent study randomized 42 patients with stroke to placebo vs. one of three doses of intravenous GSK249320, a humanized IgG1 monoclonal antibody to MAG that has a disabled Fc region. Each patient received two infusions: the first administered [24-72] hours after stroke onset, and the second, 9 days later. No safety concerns were identified [28], and a phase II proof-of-concept study is ongoing.

Numerous small molecules have also been examined to improve outcome after stroke. Small molecules may have advantages in terms of transport through the blood-brain barrier [29] and thus increased access to healthy brain areas. In many cases, candidate small molecules represent repurposed drugs, i.e., those already approved for other indications. Many of the small molecules studied for neural repair target a specific brain neurotransmitter system.

Monoaminergic drugs have been most frequently studied. An early focus was on amphetamine [30], which acts on multiple monoaminergic targets. Initial human experience in small studies was favorable [31,32], but the Subacute Therapy with Amphetamine and Rehabilitation for Stroke (STARS) study was not. This randomized, double-blind, placebo-controlled trial did not demonstrate a benefit [33]. The authors examined five weeks of twice-weekly amphetamine in 71 patients enrolled 5-10 days post-stroke. The drug was safe but did not improve the primary outcome, motor recovery over 3 months using the arm/leg Fugl-Meyer motor score [33].

A randomized, double-blind, placebo-controlled study in patients with stroke examined effects of L-Dopa and found that 100 mg L-Dopa/day (given as Sinemet and combined with physical therapy) to be significantly better than placebo on the primary endpoint, motor status by the Rivermead Motor Assessment after three weeks [34]. The authors randomized 53 patients within 6 months of stroke onset to three weeks of daily L-Dopa or placebo coupled with physiotherapy. Dopaminergic drugs have the potential advantage that measures of genetic variability may help predict inter-subject differences in treatment response [35,36]; this study awaits replication.

Serotonin is another monoaminergic neurotransmitter potentially helpful in promoting neural repair and thereby improving stroke recovery. Serotonin normally plays a role in modulating multiple cognitive functions, particularly response inhibition and memory consolidation, and modulates the impact of punishment-related signals on learning and emotion [37-39]. Early reports supported the potential clinical utility of selective serotonin reuptake inhibitor (SSRI) drugs for promoting improved motor outcome after stroke [40-43]. Recent reports suggest that increasing serotonin neurotransmission improves stroke recovery. Robinson et al [44] performed a multisite, randomized controlled trial for prevention of depression among 176 non-depressed patients enrolled within 3 months of stroke onset. Patients randomized to the placebo arm were significantly ($p<.001$) more likely to reach the primary outcome (development of major or minor depression), compared with patients in either of the two active study arms (the selective serotonin reuptake inhibitor (SSRI) escitalopram or problem-solving therapy). The strongest evidence in support of an SSRI to improve outcomes after stroke comes from The Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) study [45]. This was a double-blind, placebo-controlled trial that enrolled non-depressed hemiplegic/hemiparetic patients within 10 days of ischemic stroke onset. Patients were randomized to 3 months of oral fluoxetine (20 mg/day) or placebo. Those randomized to fluoxetine showed significantly greater gains on the primary endpoint, change in the arm/leg Fugl-Meyer motor score to day 90 ($p=0.003$), a remarkable 9.7 point difference on this 100 point scale. This

study also awaits replication.

Traditional and alternative medicines have also been studied though few using formal research methods. One exception is the Chinese Medicine Neuroaid Efficacy on Stroke recovery (CHIMES) study [46], a multicenter, double-blind, placebo-controlled clinical trial that randomized 1,100 patients to 3 months of Neuroaid vs. placebo, provided in the form of three daily doses of 4 oral capsules each. Neuroaid is a traditional Chinese medicine containing extracts of 9 herbal and 5 animal components. Patients started therapy within 72 hours of stroke onset. No difference between treatment arms was seen in the primary outcome measure, shift in the modified Rankin Scale at 3 months.

Cell-based therapies are receiving increased attention, with numerous cell types under consideration [47,48]. Most often, the strategy is to directly administer exogenous stem cells, examples of which include transformed tumor cells, adult stem cells such as marrow stromal cells, stem cells with modified genes or a bioscaffold, umbilical cord cells, placental cells, embryonic stem cells, and fetal stem cells. Such exogenous cells can be autologous, allogeneic, or xenografts. These studies are overall at an early phase.

A number of intensive activity-based therapy regimens have been studied. A key example is constraint-induced therapy, an approach that trains the affected limb while restraining the non-affected limb, in order to overcome learned disuse of the affected limb. In the EXCITE trial, constraint-induced therapy was associated with significant gains in motor outcome in 222 patients enrolled 3-9 months after stroke onset [49], with these effects enduring for years [50]. The LEAPS trial compared two therapies focused on gait in 408 patients within 2 months of stroke, and found that treadmill training with body-weight support did not differ from progressive exercise at home managed by a physical therapist in effects on walking ability 1 year after stroke [51]. While effects of these therapeutic approaches did not differ, the LEAPS trial did find that a majority of patients with stroke can experience significant behavioral gains when therapy is initiated weeks after stroke onset, with 52% of treated patients showing improved gait velocity one year after stroke onset. An intervention started on the first day post-stroke that improved gait velocity in a majority of patients 12 months post-stroke would garner great praise; this should be no less true when the therapy is initiated weeks after stroke onset.

The brain is an electrical organ, suggesting the potential for brain stimulation to promote neural repair and thereby improve outcomes after stroke. Many forms of brain stimulation have been examined, including repetitive transcranial magnetic stimulation, theta burst stimulation, epidural cortical stimulation, transcranial direct current stimulation, transcranial alternating current stimulation, and stimulation via a laser-based device [52]. There is precedence for a focus on brain stimulation, as the gold standard therapy for major depression remains a form of brain stimulation--electroconvulsive therapy [53]. Some results with brain stimulation to promote improved outcomes after stroke, mainly targeting motor outcomes, have been favorable [54,55] while others have not [56,57]. A Phase III trial aiming to improve arm motor outcomes in patients with chronic hemiparetic stroke examined neurosurgically implanted epidural cortical stimiulation + physical therapy but did not find this intervention to be significantly different from physical therapy alone [58]; post hoc analysis indicated response to brain stimulation was substantially greater among subjects with preservation of physiological integrity or with subtotal injury to key motor system anatomical structures, suggesting the ability to stratify patients to reduce trial variance and increase effect sizes [59].

Neural repair after stroke is not a one-size-fits-all undertaking. Patients vary substantially on a wide number of key covariates, each of which can significantly and substantially impact a treatment's effect size. Numerous variables have been found to be potential predictors of stroke outcome, including location and size of injury [60,61], genotype [35,62-65,] measures of brain function [66-68], and affective disorders [69,70]. Such measures may be of pivotal value in definining the population most likely to benefit from a given therapy, as stroke is a very heterogeneous condition.

References

1.Johnston SC, Hauser SL. Neurological disease on the global agenda. Ann Neurol 2008; 64(1): A11-2.

2.Writing Group M, Mozaffarian D, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016; 133(4): e38-360.

3.Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation 2010; 121(7): e46-e215.

4.Reed S, Cramer S, Blough D, Meyer K, Jarvik J. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. Stroke 2001; 32(8): 1832-40.

5.Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. Stroke 2011; 42(7): 1952-5.

6.Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008; 359(13): 1317-29.

7.Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. N Engl J Med 1995; 333(24): 1581-7.

8.Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016; 387(10029): 1723-31.

9.Cramer SC. Repairing the human brain after stroke: I. Mechanisms of spontaneous recovery. Ann Neurol 2008; 63(3): 272-87.

10.Cramer SC. Repairing the human brain after stroke. II. Restorative therapies. Ann Neurol 2008; 63(5): 549-60.

11.Zhang ZG, Chopp M. Neurorestorative therapies for stroke: underlying mechanisms and translation to the clinic. Lancet Neurol 2009; 8(5): 491-500.

12.Cheeran B, Cohen L, Dobkin B, et al. The future of restorative neurosciences in stroke: driving the translational research pipeline from basic science to rehabilitation of people after stroke. Neurorehabil Neural Repair 2009; 23(2): 97-107.

13.Knecht S, Hesse S, Oster P. Rehabilitation after stroke. Dtsch Arztebl Int 2011; 108(36): 600-6.

14.Lanfranconi S, Locatelli F, S BC, et al. Growth factors in ischemic stroke. J Cell Mol Med 2009.

15.Ringelstein EB, Thijs V, Norrving B, et al. Granulocyte colony-stimulating factor in patients with acute ischemic stroke: results of the AX200 for Ischemic Stroke trial. Stroke 2013; 44(10): 2681-7.

16.Jerndal M, Forsberg K, Sena ES, et al. A systematic review and meta-analysis of erythropoietin in experimental stroke. J Cereb Blood Flow Metab 2010; 30(5): 961-8.

17.Kolb B, Morshead C, Gonzalez C, et al. Growth factor-stimulated generation of new cortical tissue and functional recovery after stroke damage to the motor cortex of rats. J Cereb Blood Flow Metab 2007; 27(5): 983-97.

18.Belayev L, Khoutorova L, Zhao KL, Davidoff AW, Moore AF, Cramer SC. A novel neurotrophic therapeutic strategy for experi mental stroke. Brain Res 2009; 1280: 117-23.

19.Cramer SC, Fitzpatrick C, Warren M, et al. The beta-hCG+erythro poietin in acute stroke (BETAS) study: a 3-center, single-dose, open-label, noncontrolled, phase IIa safety trial. Stroke 2010; 41(5): 927-31.

20.Yip HK, Tsai TH, Lin HS, et al. Effect of erythropoietin on level of circulating endothelial progenitor cells and outcome in patients after acute ischemic stroke. Crit Care 2011; 15(1): R40.

21.Cramer SC, Hill MD. Human choriogonadotropin and epoetin alfa in acute ischemic stroke patients (REGENESIS-LED trial). Int J Stroke 2014; 9(3): 321-7.

22.Ehrenreich H, Weissenborn K, Prange H, et al. Recombinant human erythropoietin in the treatment of acute ischemic stroke. Stroke 2009; 40(12): e647-56.

23.Rivers W, Head H. A human experiment in nerve division. Brain 1908; 31: 323-450.

24.Li S, Carmichael ST. Growth-associated gene and protein expression in the region of axonal sprouting in the aged brain after stroke. Neurobiol Dis 2006; 23(2): 362-73.

25.Cheatwood JL, Emerick AJ, Schwab ME, Kartje GL. Nogo-A expression after focal ischemic stroke in the adult rat. Stroke 2008; 39(7): 2091-8.

26.Domeniconi M, Filbin MT. Overcoming inhibitors in myelin to promote axonal regeneration. J Neurol Sci 2005; 233(1-2): 43-7.

27.Buchli AD, Schwab ME. Inhibition of Nogo: a key strategy to increase regeneration, plasticity and functional recovery of the lesioned central nervous system. Ann Med 2005; 37(8): 556-67.

28.Cramer SC, Abila B, Scott NE, Simeoni M, Enney LA. Safety, Pharmacokinetics, and Pharmacodynamics of Escalating Repeat Doses of GSK249320 in Patients With Stroke. Stroke 2013; 44(5): 1337-42.

29.Pardridge WM. Drug transport across the blood-brain barrier. J Cereb Blood Flow Metab 2012; 32(11): 1959-72.

30.Feeney D, Gonzalez A, Law W. Amphetamine, Halperidol, and experience interact to affect the rate of recovery after motor cortex injury. Science 1982; 217: 855-7.

31.Crisostomo EA, Duncan PW, Propst M, Dawson DV, Davis JN. Evidence that amphetamine with physical therapy promotes recovery of motor function in stroke patients. Ann Neurol 1988; 23(1): 94-7.

32.Walker-Batson D, Smith P, Curtis S, Unwin H, Greenlee R. Amphetamine paired with physical therapy accelerates motor recovery after stroke. Further evidence. Stroke 1995; 26: 2254-9.

33.Gladstone DJ, Danells CJ, Armesto A, et al. Physiotherapy coupled with dextroamphetamine for rehabilitation after hemiparetic stroke: a randomized, double-blind, placebo-controlled trial. Stroke 2006; 37(1): 179-85.

34.Scheidtmann K, Fries W, Muller F, Koenig E. Effect of levodopa in combination with physiotherapy on functional motor recovery after stroke: a prospective, randomised, double-blind study. Lancet 2001; 358: 787-90.

35. Pearson-Fuhrhop KM, Minton B, Acevedo D, Shahbaba B, Cramer SC. Genetic variation in the human brain dopamine system influences motor learning and its modulation by L-dopa. PloS one 2013; 8(4): e61197.

36. MacDonald HJ, Stinear CM, Ren A, et al. Dopamine Gene Profiling to Predict Impulse Control and Effects of Dopamine Agonist Ropinirole. J Cogn Neurosci 2016; 28(7): 909-19.

37. Cools R, Roberts AC, Robbins TW. Serotoninergic regulation of emotional and behavioural control processes. Trends Cogn Sci 2008; 12(1): 31-40.

38. Logue SF, Gould TJ. The neural and genetic basis of executive function: attention, cognitive flexibility, and response inhibition. Pharmacol Biochem Behav 2014; 123: 45-54.

39. Cowen P, Sherwood AC. The role of serotonin in cognitive function: evidence from recent studies and implications for understanding depression. J Psychopharmacol 2013; 27(7): 575-83.

40. Dam M, Tonin P, De Boni A, et al. Effects of fluoxetine and maprotiline on functional recovery in poststroke hemiplegic patients undergoing rehabilitation therapy. Stroke 1996; 27(7): 1211-4.

41. Miyai I, Reding R. Effects of antidepressants on functional recovery following stroke. J Neuro Rehab 1998; 12: 5-13.

42. Pariente J, Loubinoux I, Carel C, et al. Fluoxetine modulates motor performance and cerebral activation of patients recovering from stroke. Ann Neurol 2001; 50(6): 718-29.

43. Fruehwald S, Gatterbauer E, Rehak P, Baumhackl U. Early fluoxetine treatment of post-stroke depression--a three-month double-blind placebo-controlled study with an open-label long-term follow up. J Neurol 2003; 250(3): 347-51.

44. Robinson RG, Jorge RE, Moser DJ, et al. Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial. Jama 2008; 299(20): 2391-400.

45. Chollet F, Tardy J, Albucher JF, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-con trolled trial. Lancet Neurol 2011; 10(2): 123-30.

46. Chen CL, Young SH, Gan HH, et al. Chinese medicine neuroaid efficacy on stroke recovery: a double-blind, placebo-controlled, randomized study. Stroke 2013; 44(8): 2093-100.

47. Lindvall O, Kokaia Z. Stem cell research in stroke: how far from the clinic? Stroke 2011; 42(8): 2369-75.

48. Savitz SI, Cramer SC, Wechsler L. Stem cells as an emerging paradigm in stroke 3: enhancing the development of clinical trials. Stroke; a journal of cerebral circulation 2014; 45(2): 634-9.

49. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. JAMA 2006; 296(17): 2095-104.

50. Wolf SL, Winstein CJ, Miller JP, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. Lancet Neurol 2008; 7(1): 33-40.

51. Duncan PW, Sullivan KJ, Behrman AL, et al. Body-weight-supported treadmill rehabilitation after stroke. The New England journal of medicine 2011; 364(21): 2026-36.

52. Edwardson MA, Lucas TH, Carey JR, Fetz EE. New modalities of brain stimulation for stroke rehabilitation. Experimental brain research 2013; 224(3): 335-58.

53. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.

54. Lindenberg R, Zhu LL, Ruber T, Schlaug G. Predicting functional motor potential in chronic stroke patients using diffusion tensor imaging. Hum Brain Mapp 2011; (in press).

55. Ackerley SJ, Stinear CM, Barber PA, Byblow WD. Combining theta burst stimulation with training after subcortical stroke. Stroke 2010; 41(7): 1568-72.

56. Levy R, Benson R, Winstein C, for the Everest Study Investigators. Cortical Stimulation for Upper-Extremity Hemiparesis from Ischemic Stroke: Everest Study Primary Endpoint Results. International Stroke Conference; 2008; New Orleans, LA; 2008.

57. Pomeroy VM, Cloud G, Tallis RC, Donaldson C, Nayak V, Miller S. Transcranial magnetic stimulation and muscle contraction to enhance stroke recovery: a randomized proof-of-principle and feasibility investigation. Neurorehabil Neural Repair 2007; 21(6): 509-17.

58. Levy RM, Harvey RL, Kissela BM, et al. Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded Everest Trial. Neuroreha bilitation and neural repair 2016; 30(2): 107-19.

59. Nouri S, Cramer SC. Anatomy and physiology predict response to motor cortex stimulation after stroke. Neurology 2011.

60. Stinear CM, Barber PA, Smale PR, Coxon JP, Fleming MK, Byblow WD. Functional potential in chronic stroke patients depends on corticospinal tract integrity. Brain 2007; 130(Pt 1): 170-80.

61. Riley JD, Le V, Der-Yeghiaian L, et al. Anatomy of stroke injury predicts gains from therapy. Stroke 2011; 42(2): 421-6.

62. Siironen J, Juvela S, Kanarek K, Vilkki J, Hernesniemi J, Lappalainen J. The Met allele of the BDNF Val66Met polymorphism predicts poor outcome among survivors of aneurysmal subarachnoid hemorrhage. Stroke 2007; 38(10): 2858-60.

63. Cramer SC, Procaccio V. Correlation between genetic polymor phisms and stroke recovery: analysis of the GAIN Americas and GAIN International Studies. Eur J Neurol 2012; 19(5): 718-24.

64. Kato M, Serretti A. Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. Molecular psychiatry 2010; 15(5): 473-500.

65. Kohen R, Cain KC, Buzaitis A, et al. Response to psychosocial treatment in poststroke depression is associated with serotonin transporter polymorphisms. Stroke 2011; 42(7): 2068-70.

66. Cramer SC, Parrish TB, Levy RM, et al. Predicting functional gains in a stroke trial. Stroke 2007; 38(7): 2108-14.

67. Wu J, Quinlan EB, Dodakian L, et al. Connectivity measures are robust biomarkers of cortical function and plasticity after stroke. Brain : a journal of neurology 2015; 138(Pt 8): 2359-69.

68. Wang LE, Fink GR, Diekhoff S, Rehme AK, Eickhoff SB, Grefkes C. Noradrenergic enhancement improves motor network connectivity in stroke patients. Ann Neurol 2011; 69(2): 375-88.

69. Lai SM, Duncan PW, Keighley J, Johnson D. Depressive symptoms and independence in BADL and IADL. J Rehabil Res Dev 2002; 39(5): 589-96.

70. Gillen R, Tennen H, McKee TE, Gernert-Dott P, Affleck G. Depressive symptoms and history of depression predict rehabilitation efficiency in stroke patients. Archives of physical medicine and rehabilitation 2001; 82(12): 1645-9.

Recent advances in the treatment and prevention of HIV-AIDS

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HIV in Los Angeles

According to the Los Angeles County Department of Public Health Annual HIV/STD Surveillance Report, there were approximately 59,960 people living with HIV in Los Angeles County at the end of 2014, including an estimated 11,052 unaware of their status or awaiting testing confirmation (1). In 2013, the most recent year for which data was available from the county, there were 1,820 new reported diagnoses of HIV. This corresponds to an incidence of 18 new infections per 100,000 people in Los Angeles County. While the rates of infection for chlamydia, gonorrhea, and syphilis have been rising over the past decade, the rate of new HIV infections has been trending downwards since about 2006. It is a public health priority to continue to reduce the incidence of HIV due to the high, lifelong burden of managing a chronic viral infection for which there is no curative treatment.

The annual LA HIV/STD Surveillance report also provides insights into who in Los Angeles is acquiring HIV and by which route of transmission. For men, sexual contact with other men is the most common route of transmission, accounting for 88% of men living with HIV in 2014, while heterosexual contact accounts for 76% of females and only 2% of males living with HIV. Injecting drug use, either alone or combined with another risk factor, accounts for 10% of men and 21% of women living with HIV. Overall, men account for 89% of people living with HIV in Los Angeles. There are marked racial disparities in the burden of HIV, both in Los Angeles (1) and throughout the United States (2). Among the diagnoses in 2013 in Los Angeles, Latinos accounted for the largest number of cases while African-Americans had the highest rate of diagnosis, is, significantly higher than other racial groups. The reasons for these disparities are multifaceted and should be addressed with comprehensive approaches, including culturally aware care (3).

Advancements in treating HIV with antiretrovirals have extended life expectancy for HIV positive individuals so that the life expectancy gap compared to uninfected control populations is closing (4, 5). As a result, the population of people living with HIV is aging. As of 2014, the median age of persons living with HIV in Los Angeles County was 48 years, compared with 41 years in 2002 (1), while the fraction of people living with HIV in Los Angeles who are age 60 years or older is currently 14% and growing. Older individuals who are HIV-positive have higher rates of comorbidities including diabetes mellitus, cardiovascular disease, bone fractures, and renal failure, similar to HIV-negative people who are chronologically ten years older (6). Age-related health screening, prevention, and treatment should take into account the patient's HIV status. The biological causes for apparent accelerated aging among people living with HIV, even with optimal antiretroviral therapy, are not fully known, but chronic inflammation is a likely suspect (7).

Treatment with Antiretrovirals

A detailed molecular understanding of the viral lifecycle has facilitated the development of multiple chemical agents capable of blocking each step of viral replication (8). The earliest developed antiretroviral drugs targeted the viral enzymes reverse transcriptase and protease, while the viral enzyme integrase has become the new favorite target due to the higher barrier to resistance and favorable therapeutic index of this class of antiretrovirals. Regardless of which part of the viral life cycle is targeted, the net effect of each antiretroviral is to block viral replication and thereby lower the load of active virus. To be effective and to prevent viral escape through evolution, the antiretrovirals are given in combination, typically three to four distinct agents. The goal of combination antiretroviral therapy (cART) is sustained virological suppression.

Since the advent of cART in the mid-1990's, nearly continuous improvements in potency, reduction of side effects, and more convenient dosing have facilitated further reductions in mortality and morbidity (5). Today, many patients can control their HIV infection with a single, well-tolerated, daily, fixed-dose combination pill. With the development of safer and more potent agents, especially the integrase inhibitors, many

Today, many patients can control their HIV infection with a single, well-tolerated, daily, fixed-dose combination pill. With the development of safer and more potent agents, especially the integrase inhibitors, many of the older antiretrovirals that were mainstays in the early days of cART have been phased out of regular use. An especially informative guide for both patients and physicians to the latest HIV drugs is published annually by the Test Positive Aware Network (TPAN) in Chicago (see Suggested Resources). The official U.S. Department of Health and Human Services treatment guidelines were last updated in 2016 for adults/adolescents and in 2017 for pediatric cases (see Suggested Resources). Looking ahead, newer antiretroviral agents continue to be developed, as well as further improvements in co-formulations and regiment simplification. For example, long-acting, slow release injectable medicines that would provide even more convenience and consistency for delivery have shown promise in early clinical trials (9).

Based on strong evidence of benefit, including two recent, large randomized clinical trials (10, 11), initiation of cART is recommended as soon as possible upon HIV diagnosis for all persons regardless of disease progression, unless specifically contraindicated. Earlier days of the HIV epidemic featured pendulum swings in the thinking about the timing of beginning antiretroviral therapy. The accumulated evidence has definitively settled the debate in favor of immediate initiation (12).

Early initiation of cART benefits not only the HIV positive patient, but also dramatically lowers the probability of transmission of HIV, as demonstrated convincingly by the HPTN052 randomized clinical trial (13) and follow-up community-based studies (14). Consider further the recent Partners study of discordant couples, in which the seropositive partner was virally suppressed with cART and the couple was engaging in on-going condomless sex (15). This study, which accumulated 1238 couple-years of follow-up, found zero cases of linked HIV transmission, with an upper limit of 0.30 transmissions per 100 couple-years of follow-up at the 95% confidence level. The bottom line is that initiating cART as early as possible and supporting the patient so that they remain consistently on cART has a dual benefit: improved health outcomes for the seropositive person and also reduced risk of transmission to seronegative people in that individual's sexual network or to people who share needles for injecting drug use with that individual.

HIV Latency and Research towards a Cure

It is important to remember that cART suppresses HIV, but does not eliminate the virus, even when the amount of virus in blood is below the limit of detection of standard clinical assays . Therefore, cART must be maintained indefinitely to avoid viral rebound from a reservoir of latently infected cells (16). Cells that are latently infected have an integrated copy of the HIV provirus in their genome, but the HIV genes are transcriptionally silent until the cells become reactivated by a mechanism that is still being elucidated. Latently infected cells do not support viral replication, and, therefore, conventional cART, which blocks viral replication, has a negligible effect on this population of cells. The identity, location, and size of this long-lived reservoir of latently infected cells is the focus of active research because purging or controlling this reservoir is believed to be essential for developing a cure for HIV (17).

One promising avenue of cure research is the so-called "shock and kill" approach in which latency reversing agents (LRA's) could be co-administered together with cART (18). The intention is that LRA's would expose latent cells by inducing them to produce viral gene products ("shock") and therefore making the latent cell vulnerable to clearance by the immune system or to cell death caused by virus itself ("kill"). Current research is directed towards identifying a LRA -- or more likely a combination of LRA's – with sufficient potency and penetrance to reactivate a high enough fraction of the latent reservoir that long-term, drug-free remission could be achieved once the reactivated cells are cleared (19). Another approach towards a cure would be to block the ability of the uninfected cells from supporting viral rebound from the reservoir. A number of gene therapy approaches to remove the susceptibility of the uninfected cells are under development (20), many of them based conceptually on the case of the Berlin patient, who was cured of HIV by an allogeneic stem-cell transplant from a donor with a homozygous deletion in the gene for CCR5, one of the HIV co-receptors (21). Other possible cure strategies include, but are not limited to, genome editing to remove integrated proviruses (22), chimeric antigen receptor T-cell therapy (23), and immunotherapy with engineered antibodies (24).

Until a curative treatment is proven safe and effective, maintaining long-term adherence to cART remains a key priority for the care of HIV positive patients. As a laboratory researcher actively searching for a cure for HIV, when I meet with people living with HIV, I always try to express a balance of my hope for an eventual cure and of the importance of meeting their present needs, especially remaining stably virally suppressed with consistent adherence to their prescribed cART regiment.

Prevention and Pre-Exposure Prophylaxis

With analogy to cART, in which more than one drug must be combined to achieve a high level of effectiveness, it has been proposed that a successful HIV prevention campaign would combine multiple evidence-based approaches together to form a highly effective prevention strategy that would include behavioral change, biomedical approaches, treatment of other STI's, social justice and human rights (25). During the past several years evidence has been accumulating to support, as part of this combination prevention strategy, the use of antiretrovirals for pre-exposure prophylaxis (PrEP) for individuals at high risk of acquiring HIV (26). This prevention modality was developed following the precedent of using antiretrovirals prophylactically to prevent HIV transmission from mother to child and to prevent transmission after occupational or non-occupational exposure (see Suggested Resources for current guidelines on these prevention tools).

Pre-exposure prophylaxis has been shown to significantly lower the risk for HIV-negative individuals who are at high risk for acquiring HIV through sexual contact or injecting drug use (26). An initial concern was the possibility that PrEP users would engage in more high risk sexual activity, thus increasing their risk for other STI's, but the accumulated evidence does not support this claim, as rates of STI's and condom use do not seem to change significantly upon initiating PrEP (27). One possible explanation is that PrEP use brings individuals into more regular contact with health care professionals who provide valuable support for making healthy choices. Another potential worry about the use of PrEP was a possible rise in drug resistance, but the available evidence demonstrates that the vast majority of drug resistance cases can be prevented by ensuring that the patient is not acutely infected with HIV prior to initiating PrEP and careful monitoring (28). Given the tremendous benefit of reducing the risk of acquiring HIV, the Centers for Disease Control and Prevention has published a comprehensive set of guidelines for the implementation of PrEP, including a decision tree for determining if a patient is a good candidate for PrEP (see Suggested Resources). The Los Angeles County Department of Public Health has also published useful guidelines and patient materials (see Suggested Resources).

Continuum of Care

For those living with HIV, the continuum of care begins with diagnosis and extends through linkage to care, retention in care, and viral suppression (29). As of the end of 2014, only about 49% of people living with HIV in the United States were virally suppressed (30). For the same time period, Los Angeles County had a slightly higher viral suppression rate of approximately 52% of individuals living with HIV (1). Even with progress being made, significant obstacles for accessing HIV care in Los Angeles remain, as documented by the LA County Navigation Program to reengage lost patients into care (31). From the study's interviews, the top ten listed barriers for HIV care were the following (in ranked order): other life priorities, lack of money, lack of transportation, drinking/using drugs, stigma, homelessness, fear someone would find out, perceived lack of need for HIV care, living between US and another country, and immigration status. Given the strong impact of these social determinants of health, it is important for physicians to build relationships with their patients that are built on trust and empathetic listening.

Local community based organizations are valuable partners who provide the critical social support services that many patients need to be successful in managing their HIV care. From my personal experience, I will highlight the work of one such agency, Foothill AIDS Project (fapinfo.org), which is an exemplar of several agencies operating in Southern California. Founded in 1987, FAP provides comprehensive services for low-income people living with HIV in Los Angeles, San Bernardino, and Riverside counties including case management, housing, support groups, mental health, substance abuse counseling, food assistance, transportation, and health education. From watching the success of FAP clients in overcoming barriers to retention in care, I have observed anecdotal evidence of the impact of FAP services, especially the formation of a community of support that counters the isolation and stigmatization that many of the clients feel in their community. In my opinion, one of the key factors in FAP's success is an ethos of welcome, non-judgment, respect, and compassion.

Suggested Resources

1. Test Positive Aware Network, 21st Annual HIV Drug Guide https://www.positivelyaware.com/hiv-drug-guide Accessed August 14, 2017.

2. U.S. Department of Health and Human Services, Clinical Guidelines for HIV/AIDS https://aidsinfo.nih.gov/guidelines Accessed August 14, 2017.

3. Centers for Disease Control and Prevention, Preventing New HIV Infections https://www.cdc.gov/hiv/guidelines/preventing.html Accessed August 14, 2017.

4.Los Angeles County Department of Public Health, Division of HIV and STD Programs http://publichealth.lacounty.gov/dhsp/ Accessed August 14, 2017.

References

1.Los Angeles County Department of Public Health, 2014 Annual HIV/STD Surveillance Report. http://publichealth.lacounty.gov/dhsp/Reports/HIV-STDsurveillanceReport2014.pdf. Published February 2016. Accessed August 2017.

2.Centers for Disease Control and Prevention. HIV Surveillance Report, 2015. vol. 27. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published November 2016. Accessed August 2017.

3.V. Stone, B. Ojikutu, M. K. Rawlings, K. Y. Smith, Eds., HIV/AIDS in U.S. Communities of Color, Springer, New York, NY, (2009).

4.H. Samji et al., Closing the gap: Increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS ONE. 8, e81355 (2013).

5.A. Trickey et al., Survival of HIV-positive patients starting antiretro viral therapy between 1996 and 2013: A collaborative analysis of cohort studies. The Lancet HIV. 4, e349–e356 (2017).

6.G. Guaraldi et al., Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin. Infect. Dis. 53, 1120–1126 (2011).

7.A. C. Hearps et al., Inflammatory co-morbidities in HIV+ individuals: Learning lessons from healthy ageing. Current HIV/AIDS reports. 11, 20–34 (2014).

8.E. J. Arts, D. J. Hazuda, HIV-1 antiretroviral drug therapy. Cold Spring Harbor Perspectives in Medicine. 2, a007161–a007161 (2012).

9.A. N. Nyaku, S. G. Kelly, B. O. Taiwo, Long-acting antiretrovirals: Where are we now? Current HIV/AIDS reports. 14, 63–71 (2017).

10.J. D. Lundgren et al., Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 373, 795–807 (2015).

11.The TEMPRANO ANRS 12136 Study Group, A trial of early antiretrovirals and isoniazid preventive therapy in Africa. N Engl J Med. 373, 808–822 (2015).

12.C. J. Sellers, D. A. Wohl, Antiretroviral therapy. Infectious Disease Clinics of North America. 28, 403–420 (2014).

13.M. S. Cohen et al., Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 365, 493–505 (2011).

14.F. Tanser et al, High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science. 339, 966–971 (2013).

15.A. J. Rodger et al., Sexual activity without condoms and risk of HIV transmission in serodifferent couples when the HIV-positive partner is using suppressive antiretroviral therapy. JAMA. 316, 171–181 (2016).

16.K. Barton, A. Winckelmann, S. Palmer, HIV-1 reservoirs during suppressive therapy. Trends in Microbiology. 24, 345–355 (2016).

17.M. J. Churchill et al., HIV reservoirs: what, where and how to target them. Nature Reviews Microbiology. 14, 55–60 (2015).

18.J. T. Kimata, A. P. Rice, J. Wang, Challenges and strategies for the eradication of the HIV reservoir. Current Opinion in Immunology. 42, 65–70 (2016).

19.C. Schwartz et al., On the way to find a cure: Purging latent HIV-1 reservoirs. Biochem. Pharmacol. (2017), http://dx.doi. org/10.1016/j.bcp.2017.07.001.

20.L. D. Petz et al., Progress toward curing HIV infection with hematopoietic cell transplantation. Stem Cells and Cloning: Advances and Applications, 8, 109–8(2015).

21.G. Hütter et al., Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. N Engl J Med. 360, 692–698 (2009).

22.Z. Huang, A. Tomitaka, A. Raymond, M. Nair, Current application of CRISPR/Cas9 gene-editing technique to eradication of HIV/AIDS. Gene Therapy. 24, 377–384 (2017).

23.M. Hale et al., Engineering HIV-resistant, anti-HIV chimeric antigen receptor T cells, Mol Ther, 25, 570-579 (2017).

24.G. Ferrari et al., Envelope-specific antibodies and antibody-derived molecules for treating and curing HIV infection. Nature Reviews Drug Discovery. 15, 823–834 (2016).

25.L. G. Bekker, C. Beyrer, T. C. Quinn, Behavioral and biomedical combination strategies for HIV prevention. Cold Spring Harbor Perspectives in Medicine. 2, a007435–a007435 (2012).

26.O. Davies, A. Ustianowski, J. Fox, Pre-exposure prophylaxis for HIV prevention: Why, what, who and how. Infectious Diseases and Therapy. 5, 407–416 (2016).

27.K. Freeborn, C. J. Portillo, Does Pre-exposure prophylaxis (PrEP) for HIV prevention in men who have sex with men (MSM) change risk behavior? A systematic review. J Clin Nurs (2017), doi:10.1111/jocn.13990.

28.U. M. Parikh, J. W. Mellors, Should we fear resistance from tenofovir/emtricitabine preexposure prophylaxis? Curr Opin HIV AIDS. 11, 49–55 (2016).

29.E. M. Gardner et al., The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clinical Infectious Diseases. 52, 793–800 (2011).

30.Centers for Disease Control and Prevention, Monitoring selected national HIV prevention and care objectives by using HIV surveillance data—United States and 6 dependent areas, 2015. HIV Surveillance Supplemental Report 2017; Vol. 22(No. 2). http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published July 2017. Accessed August 2017.

31.A. R. Wohl et al., Implementation and operational research: The Navigation Program: An intervention to reengage lost patients at 7 HIV clinics in Los Angeles County, 2012-2014. J Acquir Immune Defic Syndr. 71, e44–50 (2016).

Hyperostosis Frontalis Interna in a Breast Cancer Patient

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Introduction

Hyperostosis frontalis interna (HFI) is a benign bone lesion, manifested by the accretion of bone on the inner table of the frontal bone. It is most commonly found among postmenopausal women and is believed to be associated with prolonged hormone stimulation (1,2). We report a case of HFI initially suspected as bone metastasis as she has a history of breast cancer and increasing alkaline phosphatase levels. HFI should be recognized as a benign entity and distinguished from other disorders that involve the frontal skull bone, such as Paget's disease, acromegaly, and especially malignancy.

Case Report

JH is a 73-year-old woman who was diagnosed as having stage 1 right breast cancer with infiltrating ductal carcinoma 7 years ago. The estrogen and progesterone receptors were positive and Human Epidermal Growth Factor Receptor 2 (HER2) was negative. She was treated with breast conservation surgery, adjuvant chemotherapy, and radiation therapy followed by hormone therapy with Tamoxifen

The initial laboratory tests were not remarkable with normal CBC and comprehensive metabolic panel. The alkaline phosphatase level was normal at 87 U/L. After 5 years of hormone therapy, she stopped taking Tamoxifen 2 years ago, and she has been simply followed every 3-6 months for regular check-ups with physical examination and basic laboratory tests.

About one year ago, it was found that the alkaline phosphatase level was mildly abnormal at 108 U/L (N; 35-105). The calcium level was normal at 9.3 mg/dL. She did not complain of any symptoms such as bone pain. But she has occasional dizziness without headache. No recent history of body injury was reported. The comprehensive metabolic panel was repeated 4 months later, and the alkaline phosphatase level went up to 125 U/L. But the levels of calcium, ALT, AST and total bilirubin were all normal. At this point, ultrasound of the abdomen was done to exclude any possibility of hepatobiliary disease in search for the causes of the abnormal alkaline phosphatase level. It was not remarkable except a 12-mm simple cyst in the left lobe of the liver. About 3 months later, the alkaline phosphatase

level was rechecked. Its level was higher at 137 U/L. Interval physical examination was not remarkable. At this point, bone metastasis was of concern, and imaging studies were done:
Radionuclide bone imaging (Fig1, 2) showed increased uptake in the frontal bone bilaterally, raising a suspicion of bone metastasis. Plain bone X-ray study was recommended.
The skull X ray (Fig 3, 4) showed cortical thickening and diffuse sclerosis of calvarium bilaterally without any lytic or destructive changes, consistent with hyperostosis frontalis interna.

MRI scan of the head (Fig 5, 6) confirmed the internal bone growth in the frontal bone, but without impingement of the adjacent brain parenchyma.
Interestingly, the follow-up test of the alkaline phosphatase level done 4 months after the radiological studies returned to normal at 100 U/L.

Discussion

HFI is usually a benign incidental finding, occurring in 5-12% of general population, although the bone growth can be excessive enough to cause compression of the frontal brain tissue. (2). In this patient, the MRI scan of the head/brain showed no signs of brain compression. The bone growth is characterized by sparing of the midline; bone deposition is usually limited to the inner table of the frontal bone. Histologically, there is a widened zone of lamellar bone and there may be remodeling of the endocranial plate. The cortical bone is not affected (1). The etiology of HFI is not known, it is believed that prolonged estrogen stimulation is related to HFI. While HFI is found predominantly in postmenopausal women, men with hormonal irregularities, such as those with atrophic testes, have been noted to have HFI of variable severity (1). Prevalence of HFI increases with age (3).

In this case report, the patient had a history of breast cancer treated with 5-year-long Tamoxifen hormone therapy. Although she did not have any symptoms such as bone pain, back ache or headache, nuclear bone imaging was done to rule out bone metastasis because her blood alkaline phosphatase levels have been gradually increasing. The elevated alkaline phosphatase level could be from the abnormal hepatobiliary function. But the ultrasound of the abdomen showed no abnormal findings. The radionuclide bone imaging (Fig 1, 2) showed increased uptake in the frontal skull, raising a question of bone metastasis in the patient with a history of breast cancer. Subsequent plain skull X rays (Fig 3, 4) revealed the internal growth of frontal bone, which is consistent with hyperostosis frontalis interna. The MRI scan (Fig 5,6) showed no impingement on the adjacent frontal brain.

Interestingly, the alkaline phosphatase level returned to normal several months later. Although it is believed that prolonged estrogen exposure is considered as an important etiological factor, she has not been under the estrogen influence for the past 20 years. She had been taking Tamoxifen as an anti-breast cancer hormone therapy. Tamoxifen is a selective estrogen receptor (ER) modulator which behaves as an ER antagonist in breast tissue, but as an agonist in the uterus, bone and liver (4). Tamoxifen has been shown to strengthen the bone density in postmenopausal women (5). Many years of Tamoxifen therapy could be a contributing factor in pathogenesis of HFI in this case. It is also interesting that the alkaline phosphatase levels had been rising and stayed abnormal for almost 1 year before it returned to normal, indicating that hyperostosis frontalis interna may have a pattern of spurts of bone growth rather than a slow and gradual growth pattern. Monitoring of the alkaline phosphatase levels along with radiological studies may provide a clue about the pathophysiology of this mysterious condition.

Fig1

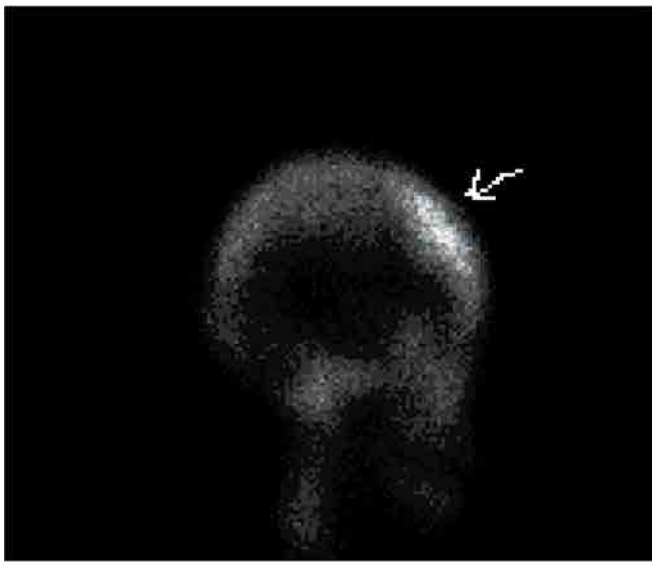


Fig 2

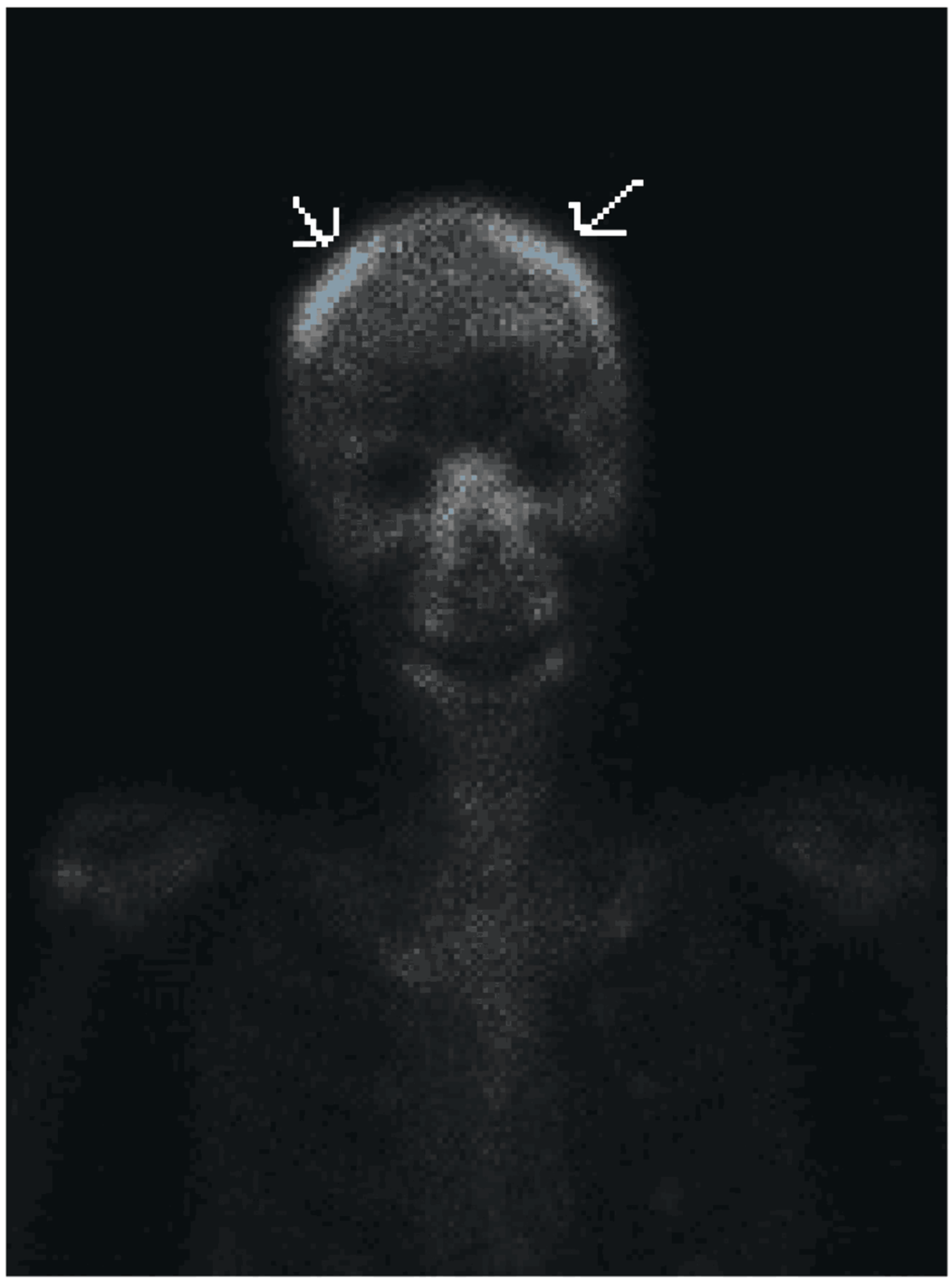


Fig 4

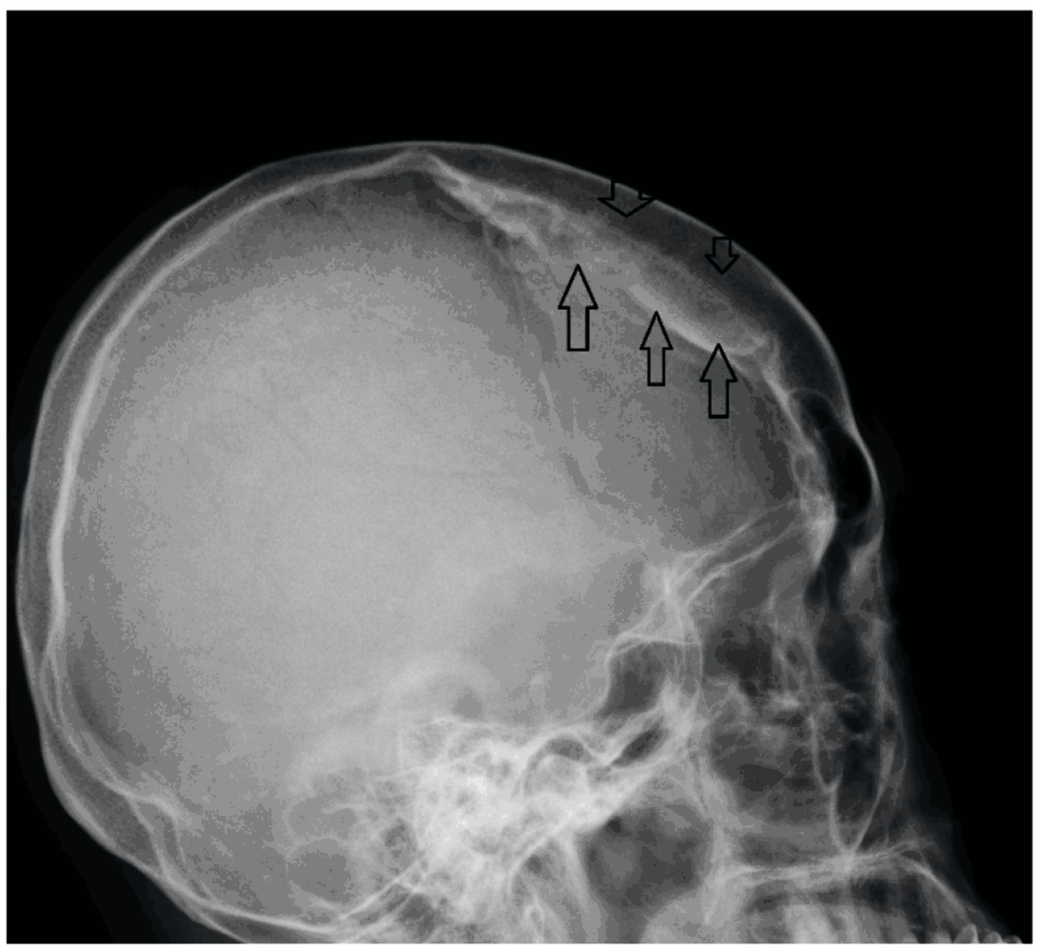


Fig 5

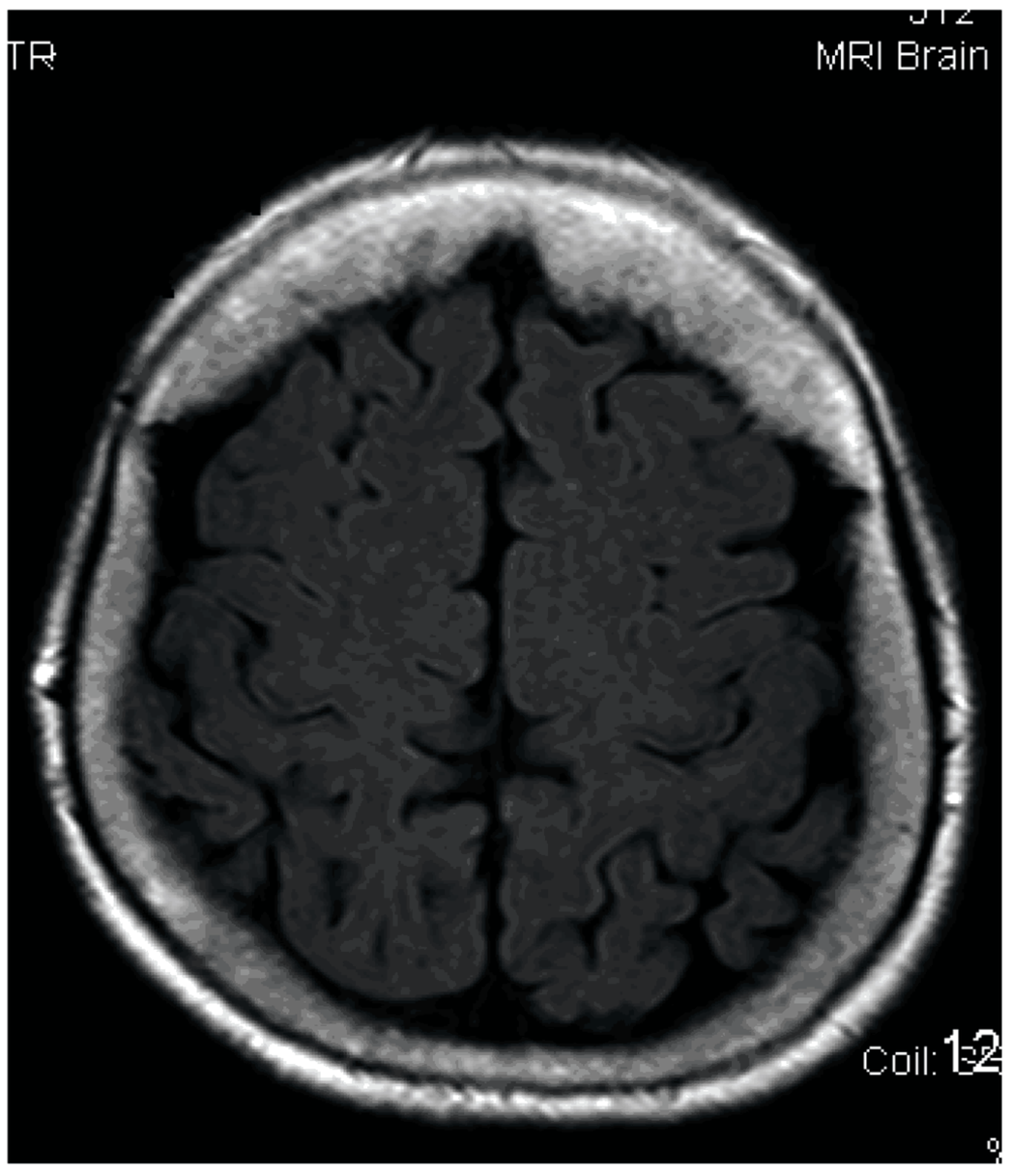


Fig 3

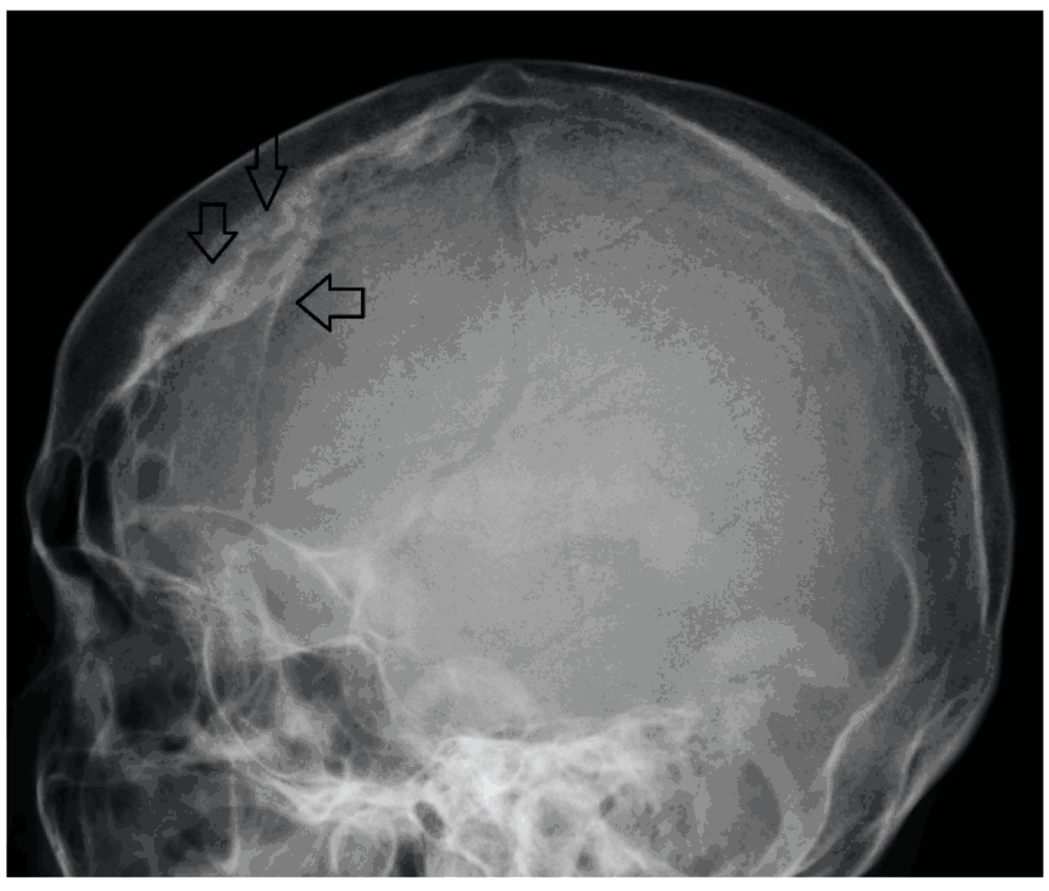
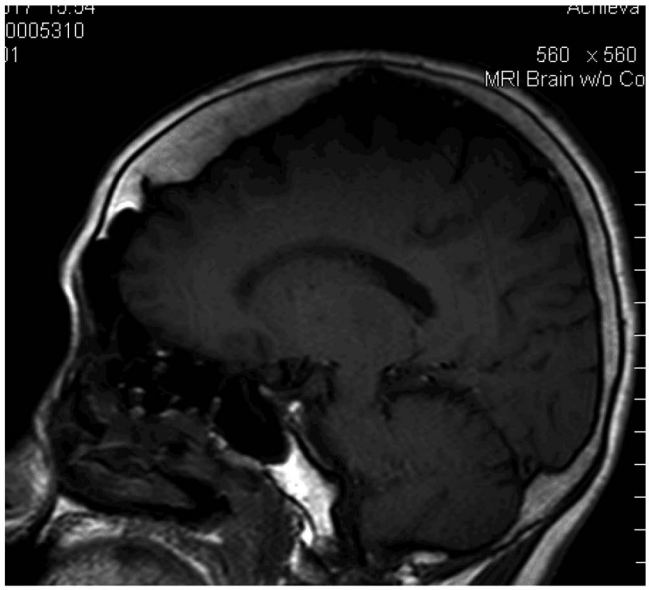


Fig 6



Reference

1.Hershkovitz I, et al., Hyperostosis frontalis interna: an anthropological perspective. Am J Phys Anthropol. 1999;109:303-25

2.She R, Szakacs J. "Hyperostosis frontalis interna: case report and review of literature". Ann. Clin. Lab. Sci. 2004;34 (2): 206–8.

3.May H, Peled N, Dar G, Cohen H, Abbas J, Medlej B, Hershkovitz I: Hyperostosis frontalis interna: criteria for sexing and aging a skeleton. Int J Legal Med. 2011 Sep;125(5):669-73

4.Riggs BL, Hartmann LC: Selective estrogen receptor modulators: mechanism of action and application to clinical practice. N Engl J Med. 2003 Feb 13;348(7):618-29

5.Powles TJ, Hickish T, Kanis JA, et al: Effect of tamoxifen on bone mineral density measured by dual-energy x-ray absorptiometry in healthy premeno pausal and postmenopausal women J Clin Oncol. 1996 Jan;14(1):78-84

Avoiding Pitfalls in Brain Death Declaration

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Introduction

The criteria for determining death by neurological criteria in adults, also known as brain death, has not changed in over twenty years, yet there continues to be high variability in practice and institutional policies nationwide as well as low compliance with recommended guidelines to establish the diagnosis. Although, to date, there are no verified reports of meaningful neurological recovery after confirmed brain death, clinicians occasionally encounter a skeptical public whose views are fueled by misguided media reports that conflate brain death with coma. In this article, we will provide a review of the literature on variability of diagnostic approaches, discuss the distinction between coma and brain death, and provide a clear, standardized approach to brain death diagnosis.

Variability in Diagnostic Approach

The diagnosis of brain death was defined in 1981 by the Uniform Determination of Death Act, which states that brain death is the irreversible cessation of all functions of the entire brain, including the brain stem and further ascertained that brain death is legally and physiologically equivalent to death, even if the heart and spinal cord continue to function. The American Academy of Neurology (AAN) set forth recommendations in 1995, with an updated revision in 2010, outlining the evidence-based guidelines for determining brain death in adults (Wijdicks, Varelas, Gronseth, & Greer, 2010). Despite this, a study by Shapell et al. (2013) looking at practice variability in brain death testing found over half of their studied population did not adhere strictly to the AAN guidelines.

There is more insight on practice variability that can be gleaned from the Shapell et al. study. For example, because certain medical conditions such as hypothermia, hypernatremia, acid-base disturbances, and other endocrine disorders can confound brain death testing, the AAN recommends excluding these toxic-metabolic derangements before initiating brain death testing. Surprisingly, these conditions were still present in approximately 25% of the brain death population studied.

There was also substantial inter-institutional variability in the clinical examination and apnea testing stipulations. For example, only 45% of the studied population had complete documentation of brainstem areflexia and absence of motor responses to pain. Although it is difficult to ascertain in the study whether this finding was due to lack of testing versus lack of documentation, the authors highlighted, at the very least, the need for improved education and documentation. Also, apnea testing was aborted or missing in up to 27% of those studied. Of that cohort without completed apnea testing, there was still 7% who did not have ancillary testing done. Furthermore, when clinicians did decide to pursue ancillary testing, there was no clear documentation to explain what prompted the decision. These findings highlight the inconsistency with which confirmatory tests are utilized and call for greater standardization of the brain death declaration process to decrease practice variability and improve adherence to published guidelines.

Words matter: Coma does not equal Brain Death

Not all patients in a coma are brain dead. The medical community, e.g. physicians, nurses, should endeavor to reserve the use of the term "brain dead" only after completion of the formal declaration process. The importance of the distinction between brain death and coma cannot be overstated because failure to recognize this difference can lead to tragic consequences and inappropriate use of these terms can contribute to the erosion of trust between medical providers and the public.

A simple, clinically useful categorization of levels of consciousness can be considered in four levels: alert, lethargic, stuporous, and comatose. Brain death is considered to be at the extreme end of this spectrum and generally implies a far worse neurological status than coma. Those who are fully alert require no stimuli to engage with the environment while those in a lethargic state need a small to moderate amount of verbal or tactile stimuli for engagement. A person who is stuporous requires deep stimuli, often in the form of pain, to elicit a meaningful, albeit brief, response. When a person reaches the level of coma, they are unconscious and unable to mount any form of meaningful response despite deep noxious stimuli. Those in a comatose state can appear brain dead until the clinician performs the critically important task of testing brainstem function. Presence of any brainstem function in an unconscious and unresponsive patient suggests that the patient is not clinically brain dead, but is in fact, in a deep comatose state.

It is also necessary to consider medical conditions that mimic a comatose state. Such diseases include locked-in syndrome, certain variants of Guillain-Barre syndrome, neuromuscular blockade, and psychogenic coma. Thorough description of these disease states is beyond the discussion of this article, however the crucial distinction between these conditions and comatose state is that the patient's consciousness may be preserved despite absence of motor function.

Although these "coma-mimicking" disease states pose a significant challenge to clinicians, greater understanding of basic concepts related to brain physiology and compensatory failure, stricter adherence to brain death testing guidelines, and greater appreciation of the variability of the brain death clinical examination, such as reflexive spinal movements, could vastly improve diagnostic accuracy and quality of clinical care.

Pathophysiology Leading to Brain Death

The Monroe-Kellie Principal provides a patho physiological basis for the sequence of events that lead to brain death. The Principal states that the pressure within the enclosed and fixed cranial vault is the result of brain tissue, arterial blood volume, cerebrospinal fluid, and venous blood volume. When pressure within the cranial vault elevates due to increased brain tissue volume or due to the introduction of a mass lesion, intracranial pressure can only remain normal as long as other components can decrease their own volume, and hence pressure.

For example, in the case of a mass lesion, there may be a decrease in either venous volume or cerebrospinal fluid to maintain an overall normal intracranial pressure. This compensatory normalization of pressure fails as that mass lesion either becomes too large or expands further to the point where no more venous or cerebrospinal fluid can be removed. Once at this point, the pressure within the enclosed vault increases swiftly. Increased pressure within the brain decreases the pressure gradient between the systemic circulation and the intracranial circulation, and this can lead to harmful reductions in cerebral blood flow. Without intervention, increased intracranial pressure eventually compromises cerebral perfusion. Widespread hypoxia and insufficient blood flow lead to neuronal death, both in the cerebral hemispheres and in the brainstem.

There is an important caveat when discussing pressure within the brain. Establishing cerebral perfusion pressure requires intracranial pressure monitoring, however not all patients with neurological compromise have intracranial pressure monitors in place, nor do they necessarily require one. Establishing cerebral perfusion pressure is not a prerequisite to brain death testing, however the AAN guidelines recommend a systolic blood pressure greater than 100 millimeters of mercury. This is not to establish high pressure within the brain as a potential contributor to neuronal death, but instead to rule out hypotension as a cause for depressed neurological function that may serve as a confounding condition, even if its presence may not itself affect brain stem function.

With elevated intracranial pressure, pathological relief of pressure occurs by means of brain tissue herniation, which then severely compromises vital structures. The basic principle of brain herniation is the displacement of brain tissue from one intracranial vault into another. Basic herniation syndromes include subfalcine herniation, transtentorial herniation, central herniation, and tonsillar herniation.

Subfalcine herniation occurs when brain tissue from the medial cerebral cortex, specifically the cingulate gyrus, herniates from one side of the cerebral cortex under the falx cerebri, then displaces into the other side. If left untreated, this type of herniation can cause altered level of consciousness followed by contralateral lower

extremity weakness.

Transtentorial herniation occurs when the uncus of the medial temporal lobe herniates through the tentorial notch, causing pressure on the diencephalon then progressively down through the midbrain, pons, and medulla. Symptoms manifest as stupor and weakening ocular eye movements then deteriorate to unresponsiveness, loss of normal motor movements and/or hemiplegia, loss of brainstem reflexes, abnormal vital signs, and eventually to cardiorespiratory arrest. Because vital structures of the brain stem are closely compacted within its enclosed space, clinical deterioration can occur rapidly without intervention.

With larger supratentorial masses or diffuse cerebral edema, bilateral uncal herniation can lead to central herniation, which is displacement of the brain stem downward through the foramen magnum. Herniation of the cerebellar tonsils through the foramen magnum can also occur, contributing to compression of the medulla and resulting in cardiorespiratory instability and death.

Diagnostic Approach to Brain Death Testing and Associated Pitfalls

When unchecked, brain tissue herniation and compromise of vital brain structures can lead to irreversible brain injury and consideration of brain death testing When delineating the diagnostic approach to brain death, institutional policies should reflect an adaptation of the guidelines set forth by the AAN. Accordingly, the following discussion will outline this approach in detail, as well as the rationale behind each step. Special attention will also be paid to pitfalls, which if not addressed, can cause misinterpretations in a critically important diagnostic process.

When it is decided to pursue brain death testing, there are a few caveats to keep in mind regarding the physicians performing the testing. First, California legislature requires two licensed physicians to independently perform and document the diagnostic process required to confirm brain death. Second, if subsequent organ donation is an option, neither of the two physicians establishing a brain death diagnosis can be involved in the donation process. Third, although only one apnea test is required, there must be two clinical exams performed by each of the physicians independently.

Acknowledging these caveats, the diagnostic approach can then be organized into four steps: establishing irreversible condition that is compatible with brain death, excluding confounding conditions, demonstrating complete loss of life-sustaining brain function, and demonstrating loss of respiratory drive. Documentation should clearly reflect each of these steps.

1. Establishing irreversibility

Establishing a clear etiology that led to neuronal death extensive enough to cause brain death should be clearly stated by the examining physicians. Examples that reflect such etiology may include devastating brain injury or hemorrhage on neuroimaging or severe anoxic brain injury, for example, due to prolonged cardiopulmonary arrest. Cortical and brainstem injury can be demonstrated by appropriate neuroimaging.

2. Excluding confounding conditions

The exclusion of confounding conditions is paramount to ensuring a valid clinical examination and avoiding pitfalls in diagnosis because such conditions may depress or otherwise limit accurate assessment of neurological function. Thus, these conditions should be addressed prior to initiating clinical testing. These confounding conditions include:

- Hypothermia defined as core temperature less than 36 degrees Celsius. Correction of hypothermia can be achieved using surface warming devices.

- Hypotension defined as systolic blood pressure less than 100 millimeters of mercury. Correction of hypotension can be achieved with volume resuscitation or vasopressors.

- Treatable metabolic disorders, which include acid-base disorders, severe electrolyte disturbances, hepatic or renal encephalopathy, endocrine dysfunction, hyper ammonemia, and severe hyperosmolar states. Medical therapies aimed at correcting these abnormalities should be attempted.

- Drug intoxication or effects, particularly narcotics, barbiturates, sedatives, and hypnotics. Exclusion of a particular drug's effect can be done by obtaining history, drug screen, calculation of clearance using 5 times the drug's half-life (assuming normal hepatic and renal function), or, if available, drug plasma levels below the therapeutic range. Note that prior use of therapeutic hypothermia, such as in cardiopulmonary resuscitation after cardiac arrest, may delay drug metabolism. Also, in the case of alcohol intoxication, it is reasonable to use the legal alcohol limit for driving, defined as 0.08%, as a practical threshold.

- Presence of neuromuscular blocking agents. There should be no recent administration or continued administration of neuromuscular blocking agents, evidenced by the presence of a train of four twitches

with maximal ulnar nerve stimulation.

In the event that correction has been attempted but not possible, ancillary testing may be considered to aid in establishing the diagnosis, however judicious usage of such testing is advised due to inherent false positive and false negative rates. More information regarding ancillary testing will be addressed later in this discussion.

3. Demonstration of complete loss of life-sustaining brain function

The complete loss of life-sustaining brain and brainstem function must be established to diagnose brain death. Although corroborating clinical history and data points are important aspects of diagnosis, the neurological exam is hallmark in determining the presence, or absence, of activity at the cerebral level as well as each level of the brainstem. Performing such an examination can be achieved using a simple, methodical approach. The following examination approach begins rostrally by assessing loss of cerebral function then proceeds assessment caudally down the brainstem by assessing loss of function from the midbrain, to the pons, and then the medulla.

The loss of function at the cerebral level involves lack of all levels of responsiveness, indicating a comatose state. Re-visiting the levels of consciousness previously described, a person who is in a coma cannot mount any kind of brain-mediated response to various degrees of stimuli. Regardless of the intensity of any verbal, tactile, or noxious stimuli presented, the comatose patient will not open or move their eyes, grimace to pain, have any facial movement, and will not demonstrate any brain-mediated motor response in any extremities.

For the purpose of brain death testing, assessment of cerebral function centers primarily on the motor examination because it would have already been established that the patient can not respond to verbal stimuli. Testing motor function starts by uncovering the patient from any bed linens, while maintaining modesty, to ensure all extremities are exposed. The clinician then places the patient's upper extremities in a neutral position by passively resting the patient's arms on their abdomen in a slightly flexed position. This is important to allow the clinician to note even the slightest motor response to noxious stimuli as subtle flexion and extension are not easy to see if the patient's arms were laying on their sides. Once in neutral position, painful stimulation can be achieved by applying deep pressure to the medial supra orbital ridge or on the condyles of the temporomandibular joint, as well as the nail beds of each extremity. A nasal tickle using a cotton swab may also be used as a form of noxious stimuli. When using any of these techniques, the clinician observes the face for any grimacing or eye movement. The extremities are also keenly observed for movement consistent with localization, flexion, or extension to pain. If present, such movements are brain-mediated and are inconsistent with brain death. Absences of these movements, however, demonstrate no response to pain and can be consistent with brain death. Additionally, the telemetry monitor should be observed for any autonomic response to pain which would not be consistent with brain death.

A pitfall associated with the motor examination is failure to use multiple stimuli in multiple locations. The clinician should not hesitate to repeat the stimuli until they are confident of their examination findings. There can, however, be spinal-mediated pain responses evidenced by triple flexion in the lower extremities. The presence of triple-flexion is still consistent with brain death due to its spinal origin, however abnormal flexion or extensor posturing in the upper extremities suggest intact corticospinal tract function and is inconsistent with brain death. The clinician should be able to recognize and differentiate spinal reflexes such as triple flexion from meaningful cerebral motor responses to pain.

After establishing absence of cerebral motor responses, brainstem function is assessed. Midbrain activity can be assessed with the pupillary light reflex. This reflex tests the afferent limb of cranial nerve II and the efferent limb of cranial nerve III. Testing is done by opening the patient's eyes in a dimly lit room, shining a bright light directly in to the eyes, and observing for response. When intact, the pupils receive the light and respond by reflexively constricting. Fixed, bilateral pupils that range from 4-9 millimeters and do not respond to bright light can be consistent with brain death. For the purpose of brain death testing, absence of pupillary response to bright light are indicative of absent midbrain function because cranial nerve III arises from the midbrain.

A pitfall associated with testing pupillary reaction is the failure to recognize constricted pupils, prior to bright light, which may indicate drug intoxication. This would trigger further investigation and prompt termination of brain death testing. Another pitfall clinicians need be aware of is anisocoria, which is not consistent with brain death because complete absence of midbrain function requires bilateral fixed, dilated pupils.

The pons and pontomedullary junction of the brainstem can be assessed with the corneal reflex and vestibulo-ocular reflex. The corneal reflex tests the afferent limb of the ophthalmic division of cranial nerve V and efferent limb of cranial nerve VII. Testing the corneal reflex is done by gently stroking the cornea with a

cotton swab to elicit a reflexive blink or eye-lid twitch. Absence of the reflexive blink or eye-lid twitch indicates absence of corneal reflex. Clinicians can avoid pitfalls by ensuring the cornea, not sclera, is stimulated by the cotton swab and also by ensuring contact lenses are not in place which may abolish response.

The vestibulo-ocular reflex (VOR) assesses cranial nerve III, VI, and VIII by assessing whether brainstem eye movement pathways are intact. There are two maneuvers to elicit this reflex in the non-responsive patient. The first maneuver, called the oculocephalic maneuver, or "Doll's eyes", involves observing the patients eyes while the clinician turns the head from one side to the other. When the VOR is intact, the eyes move in the direction opposite the head turn. When not intact, the eyes stay in a primary position regardless of which way the head is turned. Absence of this reflex is consistent with brain death.

The oculocephalic maneuver is not always the VOR test of choice, particularly when the patient has an unstable cervical spine, as can be the case with severe traumatic injuries. Another maneuver to test VOR is the oculo-vestibular reflex (also known as the Cold Caloric reflex). This reflex is tested by having the clinician inject 50mL of an ice water flush continuously, one ear at a time, for 60 seconds while holding both eyes open. The clinician then observes the eye movements for one minute to see whether they move away from the tested ear versus staying in primary position. Slow drift of the eyes towards the ear being infused with or without a compensatory fast phase nystagmoid movement in the opposite direction occurs in a patient with intact VOR. If the eyes remain in primary position, this finding represents functional absence of cranial nerves III, VI, and VIII, indicating loss of function down to the pons and pontomedullary junction. After testing one ear, the clinician then moves on to the other ear, however, clinicians must wait at least 5 minutes prior to initiating testing on the other ear. A testing pitfall in this situation is for the clinician to ensure the fast phase of eye movement is observed and also ensure that five minutes has passed before testing the opposite ear.

The medulla is assessed when the clinician attempts to elicit a pharyngeal (gag) and tracheal (cough) reflex. This tests the afferent limb of cranial nerve IX and efferent limb of cranial nerve X. Eliciting a gag reflex is done by stimulating the posterior pharynx with a cotton swab or by applying traction to the endotracheal tube. With this stimulation, the patient with an intact gag response will appear to gag or weakly cough. The cough reflex is stimulated by deep endotracheal suction. Absence of the gag and cough reflex is indicative of loss of medullary function because cranial nerve IX and X arise from the medulla.

The absence of cerebral motor response to noxious stimuli, absence of pupillary reflex to bright light, absence of corneal reflexes, absence of VOR, and absence of pharyngeal and cough reflex represents functional absence in the cerebral hemispheres and entire brainstem. An examination that includes the loss of all of these movements and reflexes, in its entirety, is an exam that fulfills almost all clinical criteria for brain death. The final step in diagnosis is the apnea test.

4. Demonstrating loss of respiratory drive

Demonstrating loss of respiratory drive is achieved with the apnea test, which assesses the lack of responsiveness to increased blood carbon dioxide concentrations. This test should be performed after other aspects of clinical examinations are completed and are deemed consistent with brain death. Absence of breathing drive is determined by measuring arterial carbon dioxide concentration prior to test initiation then comparing it to arterial carbon dioxide at 8-10 minutes after the patient is disconnected from the ventilator.

Before starting the apnea test, the patient should be normotensive, normothermic, euvolemic, eucapnic, and not hypoxic with an arterial partial pressure of oxygen greater than 200. If the patient is hemodynamically unstable, vasopressors and fluid resuscitation should be titrated to achieve a consistent systolic blood pressure greater than 100 millimeters of mercury. If high doses of vasopressors are required to achieve this goal, ancillary testing can be considered to avoid cardiopulmonary collapse during testing.

The pre-requisite for apnea testing involves pre-oxygenating the patient to an arterial partial pressure of oxygen greater than 200 and adjusting minute ventilation to achieve arterial partial pressure of carbon dioxide of 35-45. When this has been established, the endotracheal tube should be completely disconnected from the ventilator tubing and 6-8L of oxygen should be provided by using a nasal cannula placed directly inside the endotracheal tube. The clinician will then observe the patient for at least 8-10 minutes, monitoring specifically for chest and/or abdominal movements that may indicate respirations. At any point in this time period, the apnea test should be aborted if the systolic blood pressure decreases lower than 90 millimeters of mercury (allowing for active titration of vasopressors), oxygen saturation decreases to less than 85% for more than 30 seconds, or if spontaneous respirations are observed. If none of these occur and the patient is at the 8-10 minute mark, an arterial blood gas may be drawn to assess carbon dioxide retention.

An apnea test that supports the clinical diagnosis of brain death is confirmed if the arterial carbon dioxide is either greater than 60 points from baseline, or greater than 20 points above known baseline in patients with a history of pulmonary conditions that increase arterial carbon dioxide concentrations. In the case that the carbon dioxide goals were not met but the patient meets clinical criteria for brain death, the apnea test can be repeated for a longer period of time, such as 10-15 minutes in hemodynamically stable patient.

The official time of death is then documented as the time the arterial blood gas results are reported. In cases where clinical uncertainty exists, ancillary testing may be performed in accordance with national standards specific to brain death determination. In these circumstances, the time of death is when the attending physician officially signs the ancillary test.

Brain-death Associated Movements

Once brain death is established, clinicians need to be cognizant of certain spinal mediated reflexes that can occur in the brain dead body. Knowledge of these reflexes can prevent pitfalls in a brain death diagnosis and avoid confusion if family members question whether the movements are meaningful. For example, these reflexive movements may include the Lazarus Sign, manifested as bilateral arm flexion at the elbow towards the chin, followed by relaxation of the arms at the side of the body. To the untrained eye, it can appear as though the body is reaching towards the endotracheal tube. The timing of such reflexes mostly occur in the first 24 hours of brain death diagnosis, however some reflexes can be seen up to 4 days after diagnosis (Jain and DeGeorgia, 2005). There can also be undulating toe movements, facial myokymia, asymmetrical opisthotonus, spinal myoclonus, hugging-like motion, viscero-somatic reflex, head turning, and triple flexion. Numerous reflexive movements have been reported, however a comprehensive review of each reflex is not feasible within the constraints of this discussion.

Ancillary Testing

Brain death is a clinical diagnosis, therefore clinical examination and judgment remains paramount. Ancillary testing is reserved for situations where aspects of clinical testing or circumstance are called into question. Although several ancillary tests have been studied, these tests have inherent false positive and false negative rates. The only validated tests are cerebral angiography to demonstrate absence of flow in all intracranial arteries, brain perfusion single photon emission computed tomography imaging to show lack of tracer uptake on imaging indicating absence of intracranial perfusion, electroencephalogram to show electrocerebral inactivity, and transcranial doppler to confirm cerebral circulatory arrest. Of note, ancillary tests must be performed in accordance with published guidelines and employ techniques that are specific to brain death testing. Clinicians who perform and interpret these tests should be familiar with these approaches.

Avoiding Communication Pitfalls

Avoiding pitfalls in verbal and written communication can prevent confusion surrounding the diagnosis of brain death. As soon as the clinical scenario suggests possible or imminent brain death, clear verbal communication with family includes preparing them for that possibility. Providers should communicate this prior to initiating any brain death testing. It is also prudent to advise family that circulatory arrest can occur in the midst of apnea testing. Once diagnosed, it must be made clear that brain death is the same as death.

At this point, the healthcare team should avoid using terms such as comatose and unresponsive, but should instead refer to the family's loved one as deceased. When the healthcare team refers to interventions such as mechanical ventilation or vasopressor use, it should be made clear that such interventions are only supporting organs, and are no longer supporting life.

In addition to clear verbal communication, providers must be clear with documentation of brain death. Such documentation should include etiology and irreversibility of condition, exclusion of confounding conditions, all aspects of examination including ancillary testing if used, and official time of death.

Discussion

The declaration of brain death is a clinical diagnosis that relies on established criteria supported by practice guidelines. There continues to be substantial practice variability in the determination and documentation of brain death and thus there is a pressing need for clinicians to adhere to a standardized approach. Diagnostic accuracy may be improved by strict adherence to practice guidelines, improved awareness of coma-mimics, greater understanding of the pathophysiology leading to brain death, avoiding potential diagnostic pitfalls, and appreciation of spinally mediated reflexes that may occur in brain death. Further, the term "brain death" should not be used loosely or conflated to describe the myriad of conditions that may result in coma. These approaches are essential to maintain a high quality of care and to improve understanding of brain death within the medical community and general public.

References

Wijdicks, E.F., Varelas, P.N., Gronseth, G.S., & Greer, D.M. (2010). Evidence-based guideline update: Determining brain death in adults. Neurology, 74, 1911- 1918.

California Legislative Information. (1982). Health and safety code: Article 2 confirmation of death [7181-7182]. Retrieved from http://leginfo.legislature.ca.gov/faces/codes_displayText.xhtml?lawCode=HS C&division=7.&title=&part=1.&chapter=3.7.&article=2.

Jain, S. & DeGeorgia, M. (2005). Brain death-associated reflexes and automatisms. Neurocritical Care, 3, (122-126).

Shappell, C.N., Frank, J.I., Husari, K., Sanchez, M., Goldenberg, F., & Ardelt, A. (2013). Practice variability in brain death determination: A call to action. Neurology, 81, 2009-2014.

Partnering to Heal through Antibiotic Stewardship and Infection Prevention

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Background

Morbidity and mortality due to infectious diseases in the United States has been in decline since the 18th century due to improvements in sanitation, vaccination and the development of antibiotic drugs. [1] However, several developments threaten this trend including healthcare-associated infections (HAIs) and antibiotic resistance. [2] In response to this threat, various governmental and regulatory agencies now require healthcare institutions to develop and maintain infection prevention and antibiotic stewardship programs. [3,4]

Infection prevention programs are tasked with protecting patients, healthcare workers and others in the healthcare environment from infectious diseases. [4] Antibiotic stewardship programs are responsible for ensuring appropriate antibiotic use to prevent unnecessary consequences of inappropriate use. [3] Infection prevention and antibiotic stewardship programs have complimentary and overlapping objectives and interventions, thus collaboration between the two is essential for best outcomes. [3,5]

Infection Prevention and Antibiotic Stewardship at Pomona Valley Hospital Medical Center
The infection prevention and antibiotic stewardship programs at Pomona Valley Hospital Medical Center (PVHMC) were established in 1988 and 2012, respectively. In recent years, their collective goals have been to minimize the incidence of HAIs including Clostridium difficile infection (CDI), catheter-associated urinary tract infections (CAUTI) and central line-associated bloodstream infections (CLABSI), and slow or even reverse the development of antibiotic resistance.

Multi-disciplinary teams including nurses, physicians, pharmacists, environmental services staff, information services staff, laboratory staff and administrators have been assembled to address HAIs and antibiotic use at PVHMC by promoting best practice standards. To prevent CLABSI, bundles to aid in proper insertion, care and maintenance and removal of unnecessary lines have been implemented. To prevent CAUTI, interventions to promote proper catheter use, aseptic insertion and maintenance and prompt catheter removal have been executed. To prevent CDI, which has multiple etiologies,

a number of strategies have been used including stewardship of antibiotic and acid suppressant drugs, appropriate laboratory testing for CDI, use of personal protective equipment for staff and visitors and proper disinfection and environmental isolation. Another major ongoing intervention that influences all HAIs is a campaign to improve hand hygiene practices among all hospital associates.

Ensuring appropriate use of antibiotics at PVHMC has been a multi-faceted endeavor. A core element of the antibiotic stewardship program is daily rounds with an infectious diseases physician and pharmacist on patients receiving antibiotic therapy with recommendations on appropriate antibiotic use and infectious disease diagnostics provided to the primary physician. In addition to this, the program provides ongoing education of the medical and other clinical staff on appropriate use of antibiotics and provides reference resources as well.

Both the infection prevention and antibiotic stewardship programs monitor their respective outcomes including HAI rates (e.g. CDI, CLABSI and CAUTI), antibiotic resistance rates (i.e. annual antibiograms) and antibiotic utilization. These outcome metrics are invaluable to determine the effectiveness of various interventions and monitor for emerging issues.

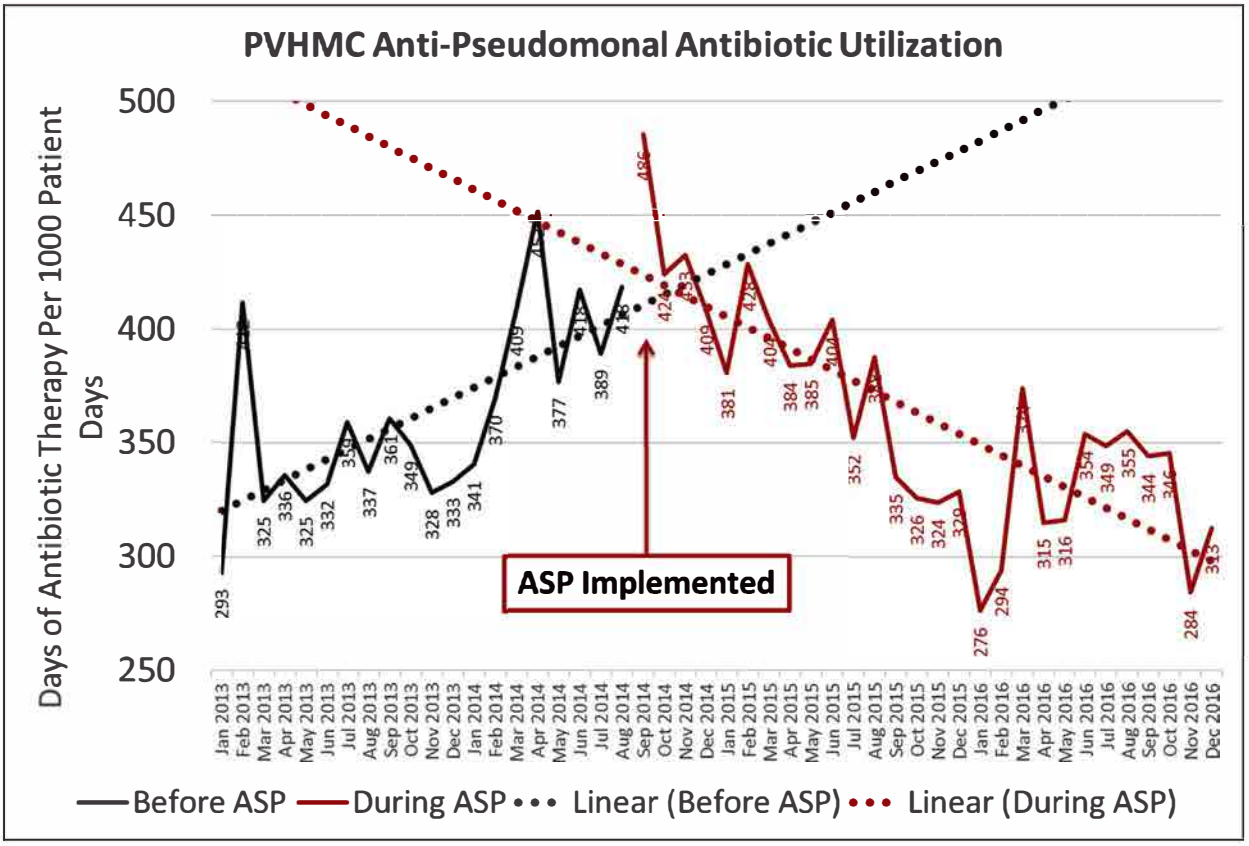
The programs have been successful in numerous ways. Substantial reductions in antipseudomonal and fluoroquinolone antibiotic use, approximately 30% and 35%, respectively have been achieved in the past 3 years (Figures 1 and 2, respectively). These reductions have been met with corresponding improvements in antibiotic susceptibility. Between 2013 and 2016, there has been a 7% and 3% improvement in fluoroquinolone susceptibility in Pseudomonas aeruginosa and Escherichia coli, respectively, and a 5% improvement in piperacillin/tazobactam susceptibility in Pseudomonas aeruginosa. CDI, CAUTI and CLABSI rates continue to be above desired levels, but newly implemented innovative multi-disciplinary approaches promise to aid in minimizing these HAIs.

Conclusion

Infection prevention and antibiotic stewardship are collaborative and complementary efforts at PVHMC to maximize the patient care quality. To fully achieve their desired outcomes, these programs require the combined efforts of all healthcare associates. Positive outcomes have been shown in recent years and continued efforts are underway to further enhance these results.

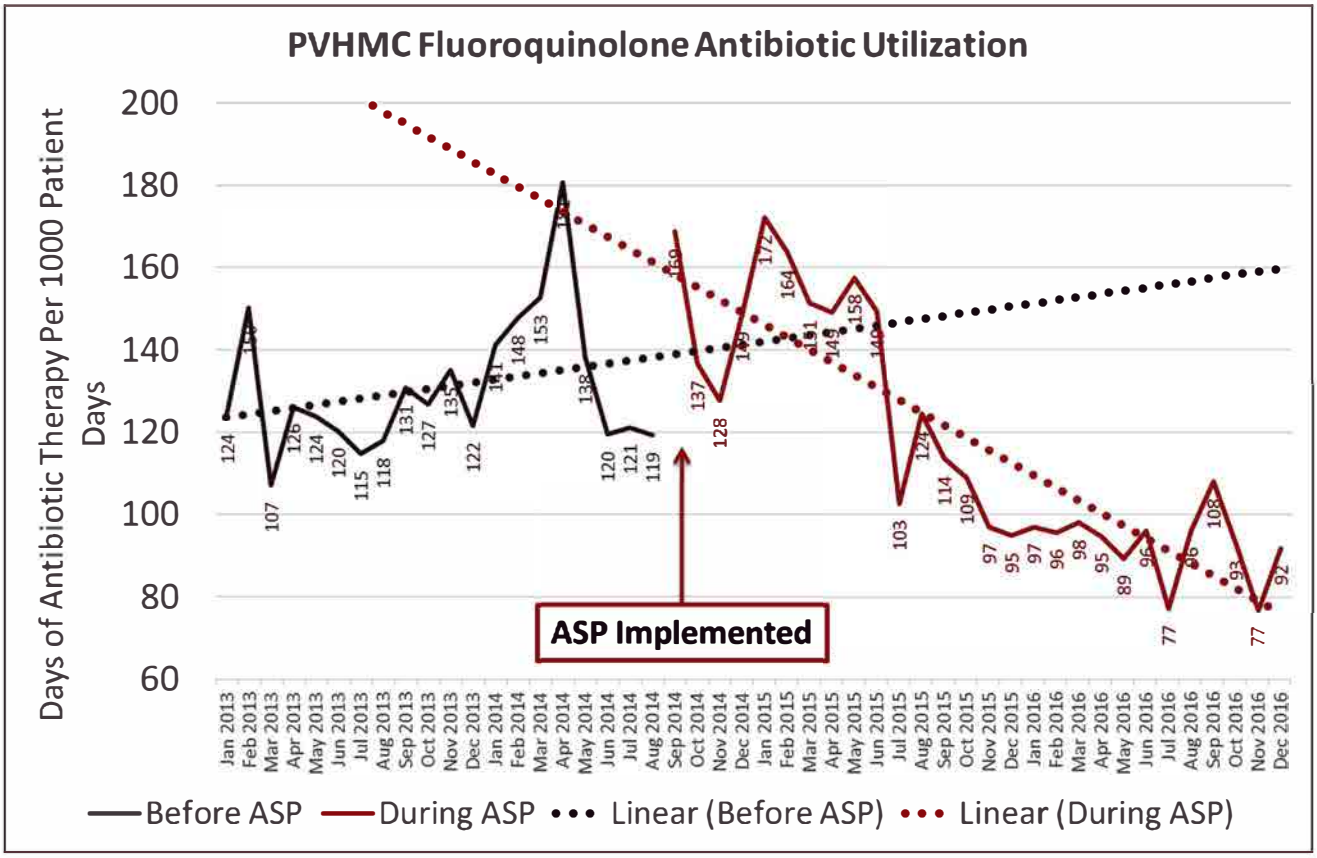
FIGURES

Figure 1. Anti-Pseudomonal Antibiotic Utilization at PVHMC 2013-2016



Footnotes: "ASP" = Antibiotic Stewardship Program

Figure 2. Fluoroquinolone Antibiotic Utilization at PVHMC 2013-2016



Footnotes: "ASP" = Antibiotic Stewardship Program

References:

1. Centers for Disease Control and Prevention National Center for Health Statistics. 75 Years of Mortality in the United States, 1935-2010. 2015. https://www.cdc.gov/nchs/data/databriefs/db88.htm#x2013;2010. Accessed September 9, 2017.

2. Centers for Disease Control (CDC). Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/

3. Centers for Disease Control (CDC). Core Elements of Hospital Antibiotic Stewardship Programs. 2014; http://www.cdc.gov-/getsmart/healthcare/pdfs/core-elements.pdf, http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed September 9, 2017.

4. Scheckler WE, Brimhall D, Buck AS et al. Requirements for Infrastructure and Essential Activities of Infection Control and Epidemiology in Hospitals: A Consensus Panel Report. Am J Infect Control. 1998 Feb;26(1):47-60.

5. Fishman N, Patterson J, Saiman L et al. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012 Apr;33(4):322-7.

Don't Forget About Dementia

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Given that more than 5 million Americans are living with dementia[1], and this number is expected to grow in coming years, most physicians can be expected to care for a substantial number of patients with cognitive impairment. The work of providing care for cognitively impaired elderly patients is a unique challenge for physicians, as their care tends to be more complex and requires additional skills and resources for the physician[2] . Evidence from prevalence studies indicates that 14% of people over age 70 have dementia[3], yet only half of those who meet criteria for a diagnosis are actually diagnosed by their physicians,. Furthermore, primary care physicians' diagnoses tend to occur much later in the disease process[4], and patients and their families are frequently not told of the diagnosis[5]. Missed and delayed diagnoses prevent early treatment, which may slow cognitive decline and prolong the period in which quality of life remains high. Earlier diagnoses and clear communication of diagnoses are associated with reduced patient anxiety, decreased caregiver burden, and allows patients and their families to make plans for the patient's eventual care needs, establish advanced directives, and to be intentional about how they spend their time[6,7].

In the aging population, it can be difficult to determine the difference between normal age-related cognitive decline, cognitive impairment, and other factors. Unfortunately, many persist in the belief that cognitive impairment is inevitable with aging. In fact, although there is an expected decline in some aspects of cognitive functioning over the lifespan (most significantly with respect to speed of processing), in general, cognition typically is well preserved through late life and does not interfere with daily functioning[8 9], .

The Alzheimer's Association recommends screening for cognitive impairment in annual wellness visits, through structured screening measures and assessment of changes in memory or ability to carry out activities of daily living, with referral for full dementia evaluations from specialists in diagnosing dementias[10]. Neuropsychological assessment is recommended to distinguish between normal age-related cognitive decline and mild cognitive impairment, to predict progression of mild cognitive impairment to dementia, and to document neurocognitive and behavioral profiles that distinguish between dementia types or between dementia and other psychiatric or cognitive deficits. Comprehensive neuropsychological assessment can also assist in management decisions in mild cognitive impairment and dementia which is important in capacity determinations, treatment considerations, and identifying levels of care needed [11,12,13]

A diagnosis of dementia is often considered to be synonymous with Alzheimer's disease (AD). Although Alzheimer's is the leading cause of dementia, equating the two often leads to a lack of recognition of other causes of significant cognitive impairment. The diagnosis of dementia (of any cause) requires that there are cognitive or behavioral symptoms which interfere with one's ability to function in everyday activities, that the deficits represent a decline from the individual's previous level of functioning, and are not explained by delirium or psychiatric conditions. Further, cognitive impairment is to be determined through a combination of information from the patient and a knowledgeable informant and an objective cognitive assessment. For a diagnosis of dementia, there must be a deficit in two domains of cognitive functioning. These domains include learning and memory, executive functioning (reasoning, decision-making, planning, sequencing activities), visuospatial abilities, language functions, and personality/behavior (e.g., agitation, impaired motivation, apathy, social withdrawal, social inappropriateness)[14]. Early

indicators of all types of dementia include a subjective experience of cognitive dysfunction by the patient or family (with mutual complaints being most predictive)[15,16].

Reversible Causes of Dementia

In the practice of medicine it is imperative that we evaluate very carefully for reversible causes of dementia. We do not want to overlook a potentially treatable condition. The most common causes of reversible dementia include pseudodementia (depression-related cognitive impairment), normal pressure hydrocephalus, chronic subdural hematomas, brain tumors, thyroid dysfunction, hypoparathyroidism, vitamin B12 deficiency, folate deficiency, thiamine deficiency, and central nervous system infections (e.g., neurosyphilis, neurocysticercosis, HIV/AIDS, chronic meningitis). The use of certain drugs, including tranquilizers, steroids, benzodiazepines, antihypertensives, and anticholinergic medications is also associated with dementia-level performance[17].

The Mnemonic "DEMENTIA" is utilized for the reversible causes of dementia.

D – Drugs
E – Eyes and Ears (visual and or hearing handicaps may be confused with dementia.
M –Metabolic (hypoglycemia, hyperglycemia, hyponatremia, hypernatremia, hypothyroidism).
E – Emotion (pseudodementia with depression)
N – Nutrient (B12 folate deficiency; normal pressure hydrocephalus)
T – Tumors (brain tumor)
I – Infections
A – Alcohol

Alzheimer's Disease

Alzheimer's disease (AD) is the most common cause of dementia. It is marked by atrophy, loss of synapses, and the accumulation of neuritic plaques consisting largely of amyloid-β and neurofibrillary tangles, which interfere with the function of neurons[18] . This process leads to the preferential destruction of the medial temporal structures with earliest changes found in the entorhinal cortex, amygdala, and hippocampus [19]. Although the exact mechanism of neuronal dysfunction is largely unknown, there is evidence that the disease process starts long before plaques begin to form and long before there are apparent clinical indicators of dementia. The onset of symptoms is insidious, and there is a course of progressive decline ultimately resulting in death. Current research indicates that AD progresses through a continuum beginning with a "pre-clinical" stage associated with the build-up of amyloid in the brain. At this stage, biomarkers may indicate disease presence, and neuropsychological testing will likely show significant changes in cognition.[20, 21] However, there is no outward evidence of cognitive impairment or difficulty performing everyday activities [22]. In the "mild cognitive impairment" (MCI)[23] stage, cognitive changes that may be noticeable to the individual or those around them but do not impact the individual's ability to live independently. However, they may rely on compensatory aids for more complex tasks. Finally, AD progresses into dementia[24] in which deficits are apparent and interfere with independent functioning.

The earliest clinical indications of an Alzheimer's process are the subjective experience of memory loss noted by the patient, especially in those with a high level of education[25,26,27] or their family and the prominent memory deficits associated with the deterioration of medial temporal structures, which is marked by rapid forgetting of newly learned information[28] . For patients ultimately determined to have AD, "memory loss," "forgetfulness," and "personality change" were the most common stated reasons for an evaluation. Early indicators included difficulty with calculations, with more than half having difficulty managing finances, decreased hygiene (e.g., less frequent bathing, wearing soiled clothing), difficulty completing tasks, frequently repeating stories, becoming lost while driving on a familiar route, and forgetting the names of familiar people. On screening evaluations, recall deficits were the most predictive [29] of AD.

Risk factors for the development of AD include genetic, environmental, and modifiable risk factors. Risk factors include apolipoprotein E type 4 allele (APOE-E4)[30] , female gender (women are twice as likely to have AD than men[31], low levels of education[32,33] a history of head injury[34], having few recreational activities [35,] depression[36] neurotic personality type [37,38] high body mass index in mid-life or late life[39,] diabetes[40], regular consumption of a high calorie diet[41], and a history of folic acid deficiency[42].

Vascular Cognitive Impairment

Vascular dementia is the second most common dementia type in the West, comprising 15-20% of dementia cases in the United States[43] and being somewhat more likely in men than women[44]. In societies where hypertension is prominent, there is a proportionally higher prevalence of vascular dementia, and forecasts of dementia prevalence anticipate that increasing trends of obesity portend a substantially higher number of dementia patients in the future[45].

Similar to the way in which the progression of AD is conceptualized as a continuum, vascular cognitive impairment (VCI) refers to the range of cognition from

prodromal vascular cognitive impairment without dementia to vascular mild cognitive impairment (VaMCI) to vascular dementia (VaD). Criteria for diagnosis of VCI from the International Society for Vascular Behavioral and Cognitive Disorders (VASCOG) includes a subjective concern of the patient or a reliable informant about a decline in cognition and objective evidence of a decline from previous level of functioning in functioning in at least one cognitive domain. Neuropsychological evaluation is ideal but screening measures that assess all cognitive domains may also be adequate. The diagnosis also requires establishment of a predominantly vascular etiology of the cognitive impairment.

VCI can take many forms and courses, as it is a group of cerebrovascular processes rather than a single disorder[47]. It can arise suddenly from macrovascular processes such as a single infarct, associated with more obvious hemimotor and hemisensory dysfunction, reflex asymmetry, aphasia, or hemiplegic gait, corresponding to the areas in which infarcts are localized. Progression may occur in a step-wise fashion from microvascular processes resulting in multiple lacunar infarcts, or there may be a more insidious onset associated with the progression of chronic ischemia in the periventricular white matter[48]. Small vessel disease tends to be associated with more subtle signs, including dysarthria, dysphagia, extrapyramidal signs, parkinsonian gait, unsteadiness, frequent falls, rigidity, and hypokinesia[49].

Not surprisingly, risk factors for VCI overlap those for stroke and coronary artery disease. A 20-year study of factors associated with cognitive impairment found that hypertension in midlife is independently associated with a steeper decline in cognition[50], which may be particularly detrimental in women, as it was associated with a 73% higher risk of dementia in females but not males[51]. The relationship between diabetes and cognitive impairment is also compelling, yielding both an increased risk of cognitive impairment and rate of cognitive decline[52]. A 20-year longitudinal study found that individuals with prediabetes had increased risk of cognitive impairment[53] over those with normal glucose and that midlife diabetes was associated with a 19% greater risk for cognitive impairment . Impaired glucose tolerance, hyperinsulinemia, and metabolic syndrome have also been identified as risk factors[54,55]. Other risk factors for VCI include atrial fibrillation[56], history of myocardial infarction[57], high levels of homocysteine[58], smoking, hyperlipidemia, peripheral artery disease, chronic kidney disease, and low cardiac output[59].

Urinary frequency, urgency, and other symptoms not explained by urological disease and gait dysfunction have been found to be among the earliest associated features of vascular dementia, preceding the development of dementia by several years[60]. Gait features may include small steps or apraxic-ataxic or parkinsonian gait. Personality and mood changes including abulia, depression, lack of initiation, and pseudobulbar affect.are also common features of VCI not typically found in AD.

Whereas memory deficits are prominent early on in the progression of Alzheimer's dementia, memory deficits tend to be more subtle and manifest later in the progression of VCI. Memory deficits in VCI are more likely to be related to retrieval inefficiency, resulting in impaired recall but retained recognition.[61,62] VCI tends to result in more prominent impairment in executive functioning and speed deficits[63,64].

Mixed Dementias

Many patients may have a combination of both Alzheimer's and cerebrovascular disease, the co-occurrence of which is termed mixed dementia and is particularly common amongst the oldest elderly patients. Some researchers suggest that mixed dementia may actually be the most common form of the disease[65], as one third of patients diagnosed with vascular dementia are found to have Alzheimer's pathology upon autopsy[66]. Similarly, the APoE e4 allele which is thought to be related to Alzheimer's pathology is also associated with cardiovascular disease. There is a high degree of overlap in etiology, as vascular risk factors are shared between the conditions[67]. The clinical presentation of mixed dementia tends to more closely resemble that of AD with more prominent memory deficits than executive dysfunction[68]. When compared to pure AD, mixed dementia patients tend to have poorer overall cognition and greater impairments in attention and visuoconstruction[69].

Lewy Body Dementia

After Alzheimer's Disease and vascular dementia, dementia with Lewy Bodies (DLB) is the third most common type of degenerative dementia. The pathological hallmark of DLB is the presence of eosinophillic intracytoplasmic inclusions, called Lewy Bodies which contain aggregates of alpha-synuclein, in the deep white cortical layers throughout the brain, especially in the anterior frontal and temporal lobes as well as the cingulate gyrus and insula[70].

Unlike Alzheimer's Disease which presents with memory loss as its first and most prominent deficit, the presentation of DLB is more similar to that of VCI, characterized by early impairment in attention, executive and visual spatial function with memory affected later in the course of the disease.[71,72,73]. Early symptoms include driving difficulty (i.e., getting lost, misjudging distances, failure to see stop signs or other cars). While the MMSE (Mini Mental Status Exam) is not a reliable test to differentiate different types of dementia, the early appearance of

impaired figure copying, clock drawing, serial subtraction, and impaired working memory is suggestive of DLB[74] .

The similarity between DLB and VCI owes to the subcortical nature of damage which preferentially impacts the subcortical-frontal circuitry. This pattern of cognitive deficits is nearly indistinguishable from that noted in Parkinson's disease dementia. The differentiating factor is often the temporal course of the relative onset of physical and cognitive symptoms. In DLB, cognitive impairment often precedes or is nearly concurrent with the onset of motor symptoms, whereas the onset of motor symptoms precedes cognitive impairment by at least a year in Parkinson's dementia[75].

In addition to dementia, distinctive clinical features of DLB include visual hallucinations, parkinsonism, fluctuations in cognition (particularly orientation), dysautonomia, sleep disorders and neuroleptic sensitivity[76] . Fluctuations in cognition and levels of alertness may occur early in the course of DLB and are estimated to be a feature in 60% to 80% of cases[77]. Episodes can be subtle as in a brief decline in the ability to perform an activity of daily living, or they may be dramatic enough to raise the question of stroke or seizure. The patient tends to "blank out" or lose consciousness, become confused, or behave in a bizarre manner. These episodes can last seconds to days and can be interspersed with periods of near normal function. This could be confusing to the clinician[78].

Visual hallucinations occur in approximately two-thirds of DLB patients but are relatively rare in AD[78,78,80,81].These symptoms are also an early sign of DLB and may precede parkinsonism. Descriptions range from well-formed images of people or animals to more abstract visions of shapes or colors. Patients have described such simple hallucinations as seeing something briefly out of the corner of their eye, or extremely complex hallucinations, such as on-going dialogue with a deceased loved one. These findings are frequently under reported[82].

REM sleep behavior disorder is a parasomnia characterized by dream enactment behavior that emerges after the loss of REM sleep atonia. Individuals have sleep related vocalization and/or complex motor behaviors during REM sleep. It may appear that they are throwing a ball or flailing to protect themselves. They range in severity from benign hand gestures to violent thrashing punching and kicking[83]. Excessive daytime sleepliness may be present. DLB patients may have obstructive and/or central sleep apnea, periodic limb movements during sleep and restless leg syndrome[84]. Transient loss of consciousness may occur. The DLB patient may also be awake but mute with a blank stare as well as having orthostatic hypotension. The symptoms may mimic Multi System Atrophy[85].

Symptoms of Pakinsonism, akinesia and bradykinesia, limb ridgity and/or gait disorder, are seen in approximately 70% to 90% of patients with DLB. Repeated falls occur in 1/3 of patients with DLB[86]. These are unprovoked[87]. Antipsychotic sensitivity can occur in up to 30% to 50% of patients with DLB[10]. These reactions can give rise to severe or irreversible Parkinsonism, impaired consciousness, and even neuromalignant syndrome. These adverse reactions may even lead to a two-to-three fold increase in mortality[88].

Summary

In the foregoing reviews of some of the most common forms of cognitive impairment seen in the elderly, the most important take home point is that not all dementias are Alzheimer's Disease and not all are irreversible. In most cases, cognitive impairment occurs on a continuum, and there is often a relatively long prodromal period of cognitive decline that precipitates apparent cognitive impairment, with early concerns by the patient and family being the most predictive of some form of cognitive decline. Early recognition of indicators of cognitive impairment can lead to earlier diagnosis and intervention earlier in the course of the disease process. Screening for cognitive impairment in those with risk factors and referral for full evaluations when possible mark good clinical practice.

References

1. Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology, 80, 1778-1783.

2. Adams, W.L., McIlvain, H.E., Geske, J.A., & Porter, J.L. (2005). Physicians' perspectives on caring for cognitively impaired elders. The Gerontologist, 45, 231-239.

3. Plassman, B.A., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weird, D.r., Ofstedal, M.B., et al. (2007). Prevalence of dementia in the United States: the Aging, Demographics, and Memory Study. Neuroepidemiology, 29, 125-132.

4. Bradford, A., Kunik, M.E., Schulz, P., Williams, S.P., & Singh, H. (2009). Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer's Disease and Associated Disorders, 23, 306-314.

5. Alzheimer's Association. (2016). Alzheimer's disease facts and figures. Alzheimer's & Dementia, 12.

6. Bradford, A., Kunik, M.E., Schulz, P., Williams, S.P., & Singh, H. (2009). Missed and delayed diagnosis of dementia in primary care: prevalence and contributing factors. Alzheimer's Disease and Associated Disorders, 23, 306-314.

7. Prince, M., Bryce, R., Ferri, C. (2011). The benefits of early diagnosis and intervention. London: Alzheimer's Disease International.

8. Salthouse, T.A. (2013). Selective review of cognitive aging. Journal of the International Neuropsychological Society, 16, 754-760.

9. Tranel, D., Benton, A., & Olson, K. (2009). A 10-year longitudinal study of cognitive changes in elderly persons. Developmental Neuropsychology, 13, 87-96.

10. Cordell, C.B., Borson, S., Boustani, M., Chodosh, J., Reuben, D., Verghese, J. et al. (2013). Alzheimer's Association recommendations for operationalizing the detection of cognitive impairment during the Medicare Annual Wellness Visit in a primary care setting. Alzheimer's & Dementia, 9, 141-150.

11. American Academy of Neurology. (1996). Assessment: neuropsychological testing of adults. Considerations for neurologists. Neurology, 47, 592-599.

12. Petersen, R.C., Stevens, J.C., Ganguli, M., Tangalos, E.G., Cummings, J.L., & DeKosky, S.T. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence-based review). Neurology, 56, 1133-1142.

13. Jacova, C., Kertesz, A., Blair, M., Fisk, J.D., & Feldman, H.H. (2007). Neuropsychological testing and assessment for dementia. Alzheimer's & Dementia, 3, 299-317.

14. McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Kawas, C.H. et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7, 263-269.

15. Gifford, K.A., Liu, D., Carmona, H., Lu, Z., Romano, R., Tripodis, Y., et al. (2015). Inclusion of an informant yields strong associations between cognitive complaint and longitudinal cognitive outcomes in non-demented elders. Journal of Alzheimers Disease, 43, 121-132.

16. Gifford, K.A., Lu, Z., Triopdis, Y., Cantwell, N.G., Palmisano, J., Kowall, N., et al. (2014). The source of cognitive complaints predicts diagnostic conversion differentially among nondemented older adults. Jornal of the Alzheimer's Association, 10, 319-327.

17. Chari, D., Ali, R., & Gupta, R. (2015). Reversible dementia in elderly: Really uncommon? Journal of Geriatric Mental Health, 2, 30-37.

18. Weiner, M.W., Veitch, D.P., Aisen, P.S., Beckett, L.A., Cairns, N.J., Green, R.C., et al. (2012). The Alzheimer's Disease Neuroimaging Initiative: a review of papers published since its inception. Alzheimers Dementia, 8 (1 Suppl), S1-68.

19. Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. Acta Neuropathologica, 82, 239-259.

20. Duke, H.S., Nguyen, C.P., Stricker, N.H., & Nation, D.A. (2017). Detectable neuropsychological differences in early preclinical Alzheimer's disease: a meta-analysis. Neuropsychology Review. https://-doi.org/10.1007/s11065-017-9345-5

21. Bondi, M.W., Jak, A.J., Delano-Wood, L., Jacobson, M.W., Delis, D.C., & Salmon, D.P. (2008). Neuropsychological contributions to the early identification of Alzheimer's disease. Neuropsychology Review, 18, 73-90.

22. Sperling., R.A., Aisen, P.S., Beckett, L.A., Bennett, D.A., Craft, S., Fagan, A.M. et al. (2011). Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7, 280-292.

23. Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C. et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7, 270-279.

24. McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Kawas, C.H. et al. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & Dementia, 7, 263-269.

25. Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kolsch, H., et al. (2010). Prediction of dementia by subjective memory impairment: Effects of severity and temporal association with cognitive impairment. Archives of General Psychiatry, 67, 414-422.

26. Van Oijen, M., Jan de Jon, F., Hofman, A., Koudstaal, P.J., & Breteler, M.M.B. (2007). Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimer's & Dementia, 3, 92-97).

27. Schultz, S.A., Oh, J.M., Koscik, R.L., Dowling, N.M., Gallagher, C.L., Carlsson, C.M., et al. (2015). Subjective memory complaints, cortical thinning, and cognitive dysfunction in middle-age adults at risk of AD. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 1, 33-40.

28. Small, B.J., Fratiglioni, L., Vitanen, M., Winblad, B., Backman, L. (2000). The course of cognitive impairment in preclinical Alzheimer disease: three and 6-year follow-up of a population-based sample. Archives of Neurology, 57, 839-844.

29. Holzer, C., & Warshaw, G. (2000). Clues to early Alzheimer's dementia in the outpatient setting. Archives of Family Medicine, 9, 1066-1070.

30. Tsai, M. S., Tangalos, E. G., Petersen, R. C., Smith, G. E., Schaid, D. J., Kokmen, E., et al. (1994). Apolipoprotein E: risk factor for Alzheimer disease. American Journal of Human Genetics, 54, 643–649.

31. Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A. (2013). Alzheimer disease in the United States (2010-2050) estimated using the 2010 census. Neurology, 80, 1778-1783.

32. Van Oijen, M., Jan de Jon, F., Hofman, A., Koudstaal, P.J., & Breteler, M.M.B. (2007). Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimer's & Dementia, 3, 92-97).

33. Evans, D.A., Hebert, L.E., Beckett, L.A., et al. (1997). Education and other measures of socioeconomic status and risk of incident Alzheimer disease in a defined population of older persons. Archives of Neurology, 54, 1399-1405.

34. Mortimer, J.A., Van Duijn, C.M., Fratiglioni, L., Graves, A.B., Heyman, A., Jorm, A.F. et al. (1991). Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. International Journal of Epidemiology, 20, S28-S35.

35. Scarmeas, N., Levy, G., Tang, M.-X., Manly, J., & Stern, Y. (2001). Influence of leisure activity on the incidence of Alzheimer's disease. Neurology, 57, 2236-2242.

36. Xu, W., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., et al. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. Journal of Neurology, Neurosurgery & Psychiatry, 86, 1299-1306.

37. Wilson, R.S., Evans, D.A., Bienias, J.L., Mendes de Leon, C.F., Schneider, J.A., & Bennett, D.A. (2003). Proneness to psychological distress is associated with risk of Alzheimer's disease. Neurology, 61, 1479-1485.

38. Terracciano, A., Sutin, A.R., An, Y., O'Brien, R.J., Ferrucci, L., Zonderman, A.B., & Resnick, S.M. (2014). Personality and risk of Alzheimer's disease: new data and meta-analysis. Alzheimer's & Dementia, 10, 179-186.

39. Xu, W., Tan, L., Wang, H.-F., Jiang, T., Tan, M.-S., Tan, L., et al. (2015). Meta-analysis of modifiable risk factors for Alzheimer's disease. Journal of Neurology, Neurosurgery & Psychiatry, 86, 1299-1306.

40. Luchsinger, J.A., Tang, M.-X., Stern, Y., Shea, S., & Mayeux, R. (2001). Diabetes mellitus and risk of Alzheimer's disease and dementia with stroke in a multiethnic cohort. American Journal of Epidemiology, 154, 635-641.

41. Mattson, M.P., (2003). Gene-diet interactions in brain aging and neurodegenerative disorders. Annals of Internal Medicine, 139, 441-444.

42. Mattson, M.P., (2003). Gene-diet interactions in brain aging and neurodegenerative disorders. Annals of Internal Medicine, 139, 441-444.

43. Plassman, B.L., Langa, K.M., Fisher, G.G., Heeringa, S.G., Weir, D. R., Ofstedal, M.B., et al. (2007). Prevalence of dementia in the United States: The aging, demographics, and memory study. Neuroepidemiology, 29, 125-132.

44. Fratiglioni, L., Launer, L.J., Breteler, M.M., Copeland, J.R., Dartigues, J.F., Lobo, A., et al. (2000). Incidence of dementia and major subtypes in Europe: A collaborative study of population-based cohors. Neurology, 54, S10.

45. Loef, M. & Walach, H. (2013). Forecast of dementia prevalence in the United States and China. Obesity, 21, E51-E55.

46. Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S.E., et al. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer's Disease and Associated Disorders, 28, 206-218.

47. Gorelick, P.B., Scuteri, A., Black, S.E., DeCarli, C., Greenberg, S.M., Iadecola, C. et al. (2011). Vascular contributions to cognitive impairment and dementia. Stroke, 42, 2672-2713.

48. Rizzi, L., Rosset, I., & Roriz-Cruz, M. (2014). Global epidemiology of dementia: Alzheimer's and vascular types. Biomed Research International, 2014, 1-8.

49. Staekenborg, S.S, van der Flier, W.M., van Straaten, E.C.W., Lane, R., Barkhof, F., & Scheltens, P. (2008). Neurological signs in relation to type of cerebrovascular disease in vascular dementia. Stroke, 39, 317-322.

50 Gottesman, R.F., Schneider, A.L., Albert, M., Alonso, A., Bandeen-Roche, K., Coker, L. et al. (2014). Midlife hypertension and 20-year cognitive change: the atherosclerosis risk in communities neurocognitive study. JAMA Neurology, 71, , 1218-1227.

51 Gilsanz, P., Mayeda, E.R., Glymour, M.M., Quesenberry, C.P., Mungas, D.M., DeCarli, C., et al. Female sex, early-onset hypertension, and risk of dementia. Neurology. http://dx.-doi.org/10.1212/WNL.0000000000004602

52. Cukierman, T., Herstein, H.C., & Williamson, J.D. (2005). Cognitive decline and dementia in diabetes –sytematic overview of prospective observational studies. Diabetologia, 48, 2460-2469.

53. Rawlings, A.M., Sharrett, A.R., Schneider, A.L.C., Coresh, J., Albert, M., Couper, D., et al. (2014). Diabetes in midlife and cognitive change over 20 years: the atherosclerosis risk in communities neurocognitive study. Annals of Internal Medicine, 161, 785-793.

54. Vanhanen, M., Koivisto, K., Kuusisto, J., Mykkanen, L., Helkala, E.L., Hanninen, T. et al. (1998). Cognitive function in an elderly population with persistent impaired glucose tolerance. Diabetes Care, 21, 398-402.

55. Solfrizzi, V., Scafato, E., Capurso, C., D'Introno, A., Colacicco, A.M., Frisardi, V, et al. (2010). Metabolic syndrome and the risk of vascular dementia: the Italian Longitudinal Study on Ageing. Journal of Neurology, Neurosurgery, and Psychiatry, 81, 433.

56. Kalantarian, S., Stern, T.A., Mansour, M., & Ruskin, J.N. (2013). Cognitive impairment associated with atrial fibrillation: a meta-analysis. Annals of Internal Medicine, 158, 338-346.

57. Sundboll, J., Hovath-Puho, E., Adelborg, K., Schmidt, M., Pedersen, L., Botker, H.E. (2017). Higher risk of vascular dementia in myocardial infarction survivors. Circulation. https://doi.org/10.1161/-CIRCULATIONAHA.117.029127

58. Welch, G.N., & Loscalzo, J. (1998). Homocysteine and atherothrombosis. New England Journal of Medicine, 338, 1042–1050.

59. Sachdev, P., Kalaria, R., O'Brien, J., Skoog, I., Alladi, S., Black, S.E., et al. (2014). Diagnostic criteria for vascular cognitive disorders: a VASCOG statement. Alzheimer's Disease and Associated Disorders, 28, 206-218.

60. Kotsoris, H., Barclay, L.L., Kheyfets, S., Hulyalkar, A., & Dougherty, J. (1987). Urinary and gait disturbances as markers for early multi-infarct dementia. Stroke, 18, 138-141.

61. Lafosse, J.M., Reed, B.R., Mungas, D., Sterling, S.B., Wahbeh, H., & Jagust, W.J. (1997). Fluency and memory differences between

ischemic vascular dementia and Alzheimer's disease. Neuropsychology, 11, 514-522.

62. Tierney, M.C., Black, S.E., Szalai, J.P., Snow, W.G., Fisher, R.H., Nadon, G. et al. (2001). Recognition memory and verbal fluency differential probable Alzheimer disease from subcortical ischemic vascular dementia. Archives of Neurology, 58, 1654-1659.

63. Looi, J.C., & Sachdev, P.S. (1999). Differentiation of vascular dementia from AD on neuropsychological tests. Neurology, 11, 670-678.

64. Vasquez, B.P., & Zakzanis, K.K. (2015). The neuropsychological profile of vascular cognitive impairment not demented: a meta-analysis. Journal of Neuropsychology, 9, 109-136.

65. Riley, K.P., Snowdon, D.A., & Markesbery, W.R. (2002). Alzheimer's neurofibrillary pathology and the spectrum of cognitive function: findings from the Nun study. Annals of Neurology, 51, 567-577.

66. Kalaria, R.N., & Ballard, C. (1999). Overlap between pathology of Alzheimer disease and vascular dementia. Alzheimers Disease and Associated Disorders, 13, S115.

67. Gorelick, P.B. (2004). Risk factors for vascular dementia and Alzheimer disease. Stroke, 35, 2620.

68. Chui, H.C., & Ramirez-Gomez, L. (2015). Clinical and imaging features of mixed Alzheimer and vascular pathologies. Alzheimer's Research & Therapy, 7, 21.

69. Dong, Y., Gan, D.Z., Tay, S.Z., Koay, W.I., Collinson, S.L., Hilal, S., et al. (2013). Patterns of neuropsychological impairment in Alzheimer's disease and mixed dementia. Journal of the neurological sciences, 333, 5-8.

70 McKeith, I.G., et.al. (2017) Diagnosis and Management of Dementia with Lewy Bodies. Neurology, 89, p. 88.

71. Salmon, D.P., et al. (1996). Neuropsychological Deficits Associated with Diffuse Lewy Body Dementia. B COGN. 31; p. 148.

72. McKeith, I.G., et.al. (2017) Diagnosis and Management of Dementia with Lewy Bodies. Neurology, 89, p. 88.

73. Kemp, J., Philippi, N., Phillips, C., Demuynch, C., Albasser, T., Martin-Hunyadi, C., et al. (2017). Cognitive profile in prodromal dementia with Lewy bodies. Alzheimer's Research and Therapy, 9. https://doi.org/10.1186/s13195-017-0242-1.

74. McKeith, I.G., et.al. (2017) Diagnosis and Management of Dementia with Lewy Bodies. Neurology, 89, p. 88.

75. Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y. et al. (2007). Clinical diagnostic criteria for dementia associated with Parkinson's disease. Movement Disorders, 22, 1689-1707.

76. McKeith, I.G., et.al. (2017) Diagnosis and Management of Dementia with Lewy Bodies. Neurology, 89, p. 88.

77. McKeith, I.G., et.al. (1996). Consensus Guidelines for the Clincal and Pathologic Diagnosis of Dementia with Lewy Bodies. Neurology. 47; p.1113.

78. McKeith, I.G., et.al. (1996). Consensus Guidelines for the Clincal and Pathologic Diagnosis of Dementia with Lewy Bodies. Neurology. 47; p.1113.

79. Ala, T.A., et.al. (1997). Hallucinations and Signs of Parkinsonism Help Distinguish Patients with Dementia and Cortical Lewy Bodies from Patients with Alzheimer's Disease at Presentation: A Clinical and Pathological Study. J. Neurol Neurosurg Psychiatry. 62; p.16

80. Galvin, J.E. et.al. (2006). Clinical Phenotype of Parkinson Disease Dementia. Neurology. 67; p.1605

81. Cagnin, A., et.al. (2013). Clinical and Cognitive Correlates of Visual Hallucinations in Dementia with Lewy Bodies. J. Neurol Neurosurg Psychiatry. 84; p.505.

82. Up to Date. (2017). Clinical Features and Diagnosis of Dementia with Lewy Bodies. (On Line Internet Subscription).

83. Paparrigopoulos, T.J. (2005). REM Sleep Behavior Disorder; Clinical Profies and Pathophysiology. INT REV Psychiatry. 17; p.293.

84. Boeve, B.F. (2002). Current Management of Sleep Disturbances in Dementia. Curr Neurol Neurosci Rep. 2: p.169.

85. Thaisetthawatkulk, P. et.al. (2004). Autonomic Dysfunction in Dementia with Lewy Bodies. Neurology. 62; p. 1804.

86. Burn, D.J., et.al. (2006). Motor Subtype and Cognitive Decline in Parkinson's Disease with Dementia, and Dementia with Lewy Bodies. J. Neurol Neurosurg Psychiatry. 77; p. 585

87. Barber, R., et.al (2001). Dementia with Lewy Bodies; Diagnosis and Management. INT J GERIATR Psychiatry. 16 (Suppl 1: S 12).

88. McKeith, I. et.al. (1992) Neuroleptic Sensitivity in Patients with Senile Dementia of Lewy Body Type. BMJ. 305; p.673.

Letter to Editor:
A simple method of medical photo taking

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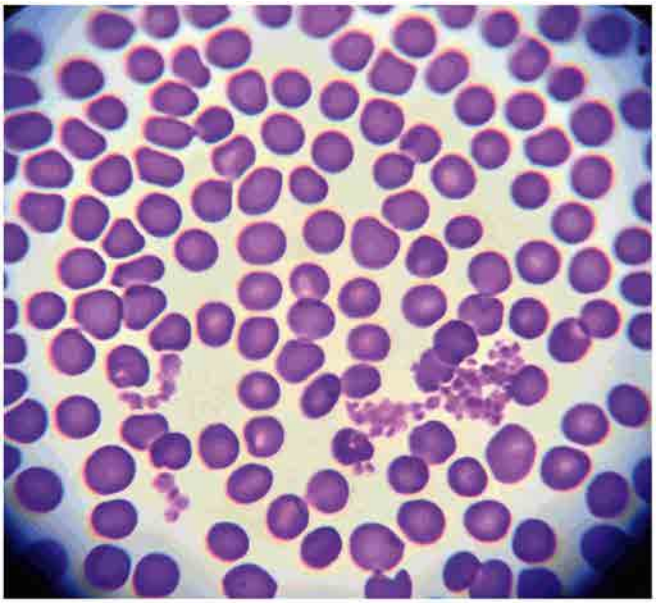
Dear Editor:
In hematology practice, reviewing the slides of peripheral blood or bone marrow smears is essential to accurately diagnose blood disease. Although their images can be photographed by a high quality digital microscope, its process still takes several steps, especially when you want to send the photographed images to colleagues. And the cost of acquiring the high quality digital microscope is high.

I would like to introduce a method of medical photography taking without special equipment. It involves an ordinary optical microscope and a smart phone, such as I-Phone or Samsung phones.
By placing the phone camera lens on one of the viewfinders of the microscope (Fig 1), you can see the bright images of the slide. Using the zooming-in function of the phone screen, you can focus the images. Then simply snap the shutter. I found this medical photo taking very interesting and funny. It is also very simple, quickly being able to send the images to colleagues.

The images of the peripheral blood smear obtained by using the above method is shown (Fig 2). The patient of this medical photo came to the office with a platelet count of 800 k/uL. The photo shows sheets of platelets suggestive of essential thrombocythemia.
I hope this simple method of medical photography taking being used widely so that medical information can be shared among colleagues more easily.

Fig 1

Fig 2



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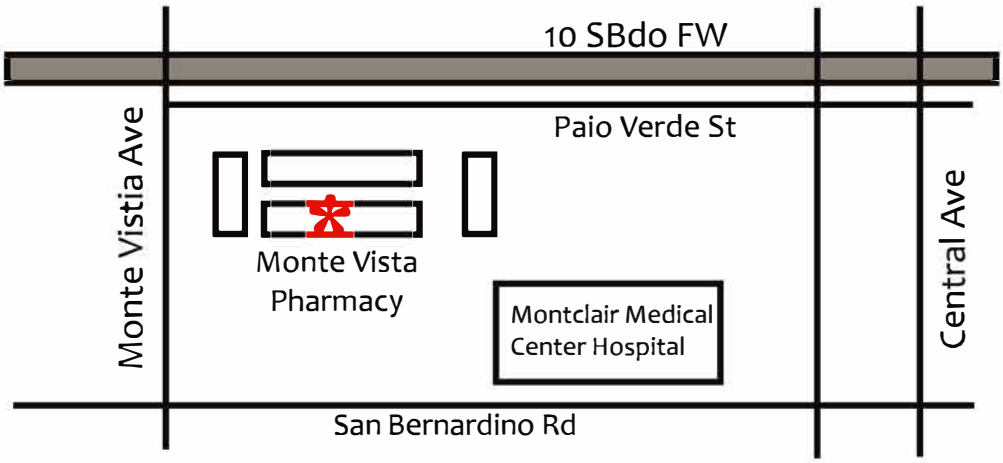

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