A. Rae-Grant, M.D.
- Staff Neurologist, Mellen Center for MS
- Acting director, Center for Brain Health (Cleveland).

"....we should not be too fastidious about where great ideas come from. Ultimately, they all come from a wrinkled organ that at its healthiest has the color and consistency of toothpaste, and in the end only withers and dies."
— Alice W. Flaherty (Neurologia)
Board Simulation in Neurology

- ‘From reading too much, and sleeping too little, his brain dried up on him and he lost his judgment.’

Miguel de Cervantes
Ms. Dementieva is a 65 year old former world class tennis player with a 2 year progressive course of memory impairment for recent events and conversations. She has trouble with her bills and bounces checks. She sometimes leaves the stove on at home.

Which diagnosis is this most consistent with?
A. Alzheimer disease
B. Lewy body disease
C. Mild cognitive impairment
D. AAMI
E. Wilson’s disease

A. Alzheimer disease
Dementia

- dementia - clinical syndrome of acquired impairment in neuropsychologic and behavioral areas sufficient to impair social or occupational functioning, including change in:
  - short- and long-term memory
  - language
  - speech
  - visuospatial ability
  - mood and personality
- mild cognitive impairment - cognitive decline greater than expected based on age and education level, but which does not interfere with activity of daily living
- delirium - transient, usually reversible, confusional state


Alzheimer disease

- Most common form of dementia
- Deposition of plaques and tangles in brain
- Amyloid deposition
- Inflammatory component? Vascular component?
- Mechanism unknown.
- No treatment alters disease course.
  - Acetylcholinesterase inhibitors modest improvements on cognitive measures.
  - Memantine moderate AD modest benefit.

Concurrent diabetes, hypertension shorten survival times.
Lewy Body Disease

- Early gait disorder
- Day to day fluctuation
- Visual hallucinosis (people in the house)
- Sensitive to antipsychotics
- Parkinsonism
- Associated with REM behavior disorder.
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Related questions

- Ms. Mala Prop has a 2 year progressive difficulty finding words, reduced verbal fluency, and spared cognitive function otherwise. MRI shows some left hemisphere atrophy.
- Best diagnosis:
  A. Posterior cortical atrophy
  B. CJD
  C. Progressive non fluent aphasia
  D. Semantic aphasia
  E. Lupus
Related questions

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Progressive aphasias

- Progressive language disorders
- Pathologically focal atrophy and neuron loss dominant hemisphere
- May have altered SPECT scan with focal hypometabolism.
- PNFA typically associated with FTLD pathology
- There are other terms people use (variety). *Fugeddaboutit.*
Creutzfeldt-Jakob Disease

- Prion disease
  - infectious protein
  - altered conformation of a normal protein, which then promotes the same conformational change in additional molecules of the same protein
- Dementia evolves over weeks to months
  - distinguish from vasculitis, encephalitis, etc.
- Pathology: 'spongiform' changes
- 2 stages: insidious, then rapidly progressive
  - mean duration from onset to death: 3-6 months
- New-Variant CJD:
  - median age of onset 29 years
  - secondary to direct transmission from infected cattle
- Diagnosis: typical EEG changes, CSF for 14-3-3- protein, changes on MRI
- Treatment: none
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Case: Ms. Gota Megrim

A 35 year-old woman presents with twice a week pounding headaches associated with episodes of migratory numbness in her left hand and around her mouth and visual blurring. She had similar headaches in the past but has an increased frequency the past 4 months. Medications include levothyroxine and BCP; Smoker 1ppd x 15 years.

- What is the best diagnosis for her recurrent headaches?
  - a. sinus headaches
  - b. tension type headaches
  - c. migraine headaches without aura
  - d. migraine headaches with aura
  - e. none of the above
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Migraine

- Migraine:
  - 4-72 hours in duration
  - Usually unilateral, pulsating, moderate-severe pain
  - Aggravated by routine activity (walking, climbing stairs)
  - nausea/vomiting, photophobia, and phonophobia common
  - Patients typically seek a quiet, dark room
- Auras – 20% of migraines. Last 5-60 minutes.
  - visual most common:
    - positive: flickering lights, spots, lines (‘zigzag’) or negative
    - reversible sensory symptoms: pins/needles, numbness
    - speech difficulties, ataxia, vertigo, diplopia, bilateral visual field loss suggest basilar migraine
    - auras can occur without headache
Headache Red Flags:

- sudden onset
- precipitated by Valsalva maneuver (cough, sneeze)
- new headache (especially age>50 – consider temporal arteritis)
- wakes patient from sleep (although migraines are common 4-9am)
- systemic symptoms, i.e. weight loss
- presence of systemic disease (i.e. malignancy, HIV)
- progressively worsening
- abnormal neurologic exam
- “Worst, first”

Migraine – Treatment

- Acute treatment:
  - Triptans: 5HT-1B/1D receptors – first-line therapy
    - almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, rhubarbitriptan...
    - contraindicated in ischemic cardiac disease
  - Anti-emetics: prochlorperazine, chlorpromazine, metoclopramide
  - NSAIDS: aspirin, naproxen, ibuprofen
  - Ergots: dihydroergotamine, ergotamine
- Avoid whenever possible, due to lower efficacy, rebound, and addiction
  - Opioids
  - Combination: caffeine, butalbital, isometheptene
  - NOTE: FIORINAL REMOVED FROM MARKET IN CANADA, EUROPEAN COUNTRIES
Migraine, Prevention

- Consider preventive therapy when:
  - significant interference with daily activities
  - > 2 headaches days per week
  - failure, intolerance, or overuse of acute therapies
  - increased risk of complications from migraine
    - basilar migraine
    - prolonged aura
    - previous migraine infarction
  - Preventative therapies: beta-blockers, tricyclics, anti-epileptic agents, SNRIs
  - Calcium blockers of limited benefit in migraine
  - Avoid triggering foods, drink, assess for sleep disorders, ‘stress’

Tension-type Headaches

- Bilateral, pressing/tightening pain
  - nausea, photophobia, and phonophobia are uncommon

- Chronic daily tension-type headache
  - present >50% of days
  - Usually affects daily life significantly

- Treatment approaches:
  - Look for rebound headaches
  - To prevent rebound, limit abortive medications to ~2-3 days per week
    - Use NSAIDS, metoclopramide, neuroleptics
    - Preventive medications
    - Rx co-morbid conditions – psychiatrist, psychologist
    - Behavioral Approaches
    - Avoid COFFEE and DIET Soft drinks.
LOUIS DEWEY, ESQ.,
OF DEWEY, CHEATHAM, AND HOWE

A prominent local plaintiff’s lawyer presents to you in the ED with acute right-sided weakness and speech difficulty. Medical history is notable for long-standing smoking, hypertension, diabetes, and stable angina. On exam, BP 190/100, right hemiparesis, decreased attention, aphasia. His son, Huey, is at the bedside taking notes. A small bead of sweat emerges on your brow.

Which of the following is the most likely diagnosis:

- a. hyperglycemia
- b. ischemic stroke
- c. partial seizure
- d. brain tumor
- e. subdural hematoma
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Louis’ CT Scan
You suspect an acute ischemic stroke.
Blood pressure is now 160/97.
It is now 3.5 hours since onset of his symptoms.

Acute management would include which of the following:

- a. brain MRI to exclude bleeding
- b. treatment to lower blood pressure
- c. consideration of IV t-PA
- d. echocardiogram to evaluate for previous MI
- e. contact your attorney
Secondary Stroke Prevention

Risk factor control
- Long-term BP control: SBP<130, DBP<80
  - ACE-inhibitors and diuretics are excellent choices
- Lipids
- Diabetes

Antiplatelet agents:
- Aspirin; clopidogrel; aspirin/dipyrimadole

Carotid endarterectomy
- Good surgeon (<6% complication): decreases risk of stroke and death when 70-99% carotid diameter stenosis.
- Stenting is another option, particularly for high-risk patients (age, diabetes, CAD, pulmonary compromise).

Embolic source: chronic anticoagulation

Hypercoagulable state – long-term treatment remains controversial

Carotid Artery Stenting vs Carotid Endarterectomy: Meta-analysis and Diversity-Adjusted Trial Sequential Analysis of Randomized Trials

“Data Synthesis: We identified 13 randomized clinical trials randomizing 7477 participants. Carotid artery stenting was associated with an increased risk of periprocedural outcomes of death, MI, or stroke (odds ratio = 1.31; 95% confidence interval, 1.08-1.59), 65% and 67% increases in death or stroke and any stroke, respectively, but with 55% and 85% reductions in the risk of MI and cranial nerve injury, respectively, when compared with CEA.”
Ms. Paris Tysia, 33-year-old right handed woman has a 5 day numbness progressing up from her toes to the bra line bilaterally. She develops trouble urinating and unsteady gait. Her past health is unremarkable. Her exam shows brisk reflexes in the legs, upgoing toes, and reduced pin sensation below T5 bilaterally. One year ago she lost vision in her left eye for 3 weeks.

- Her diagnosis is most likely:
  - A. Guillain Barre
  - B. Guillain Bar B
  - C. Multiple Sclerosis
  - D. Poliomyelitis
  - E. Hysteria
Multiple Sclerosis

- Chronic, idiopathic, recurrent inflammatory disorder: brain, spinal cord, and optic nerves
- Leading cause of non-traumatic disability in young adults
- Diagnosed through clinical and radiological criteria
  - Multiple episodes of CNS inflammation, separated in time and space
- Majority of patients have typical findings on brain and spine MRI
  - small “spots” on brain MRI are non-specific
  - additional testing can include: visual evoked potentials, lumbar puncture, blood testing for other disorders.

Treatment – 3-pronged

1. Relapses:
   - Intravenous methylprednisolone (i.e. 1g/d x3-5d), with or without prednisone taper
   - Not long term answer
2. Underlying disease:
   - Multiple FDA-approved therapies reduce relapses, may slow disability
   - most use needles (subcutaneous, intramuscular, intravenous)
   - interferons: (three flavors) –shift to Th1 anti-inflammatory immune status.
     - Toxicity: hepatic, anemic, flu-like symptoms (tx with NSAIDS), depression
   - glatiramer acetate: polypeptide which alters antigenic response
     - Toxicity: skin reactions, idiosyncratic chest pain syndrome
Multiple Sclerosis

2. Underlying disease
- fingolimod - FDA approved September 2011
  - Oral agent, blocks lymphocyte exit from nodes
  - Reduces relapse rate, progression
  - Multiple side effects: bradycardia 1st dose, bronchitis, lfts, etc.
  - Potential increase in infections
- natalizumab - monoclonal antibody, cell adhesion inhibitor
  - progressive multifocal leukoencephalopathy 1:1000
  - anaphylaxis 1:50 hypersensitivity reactions; rare liver toxicity
  - JC virus testing available to risk stratify.

3. Symptom management
Spasticity:
  - Stretching, baclofen, tizanidine, gabapentin
Sensory disorders – bothersome paresthesias
  - gabapentin, tricyclics, duloxetine
Depression:
  - common
  - may be increased by interferons
Fatigue:
  - Routine aerobic exercise program
  - Amantadine
  - Modafinil

Extended release Dalfampridine: FDA approved to speed walking in MS: cost $1000 per month, Efficacy mild; about 30% may respond.
A 58-year-old man in your clinic reports hand tremor which has increased for the past 5 years. Tremor is noticed when holding a cup of coffee, improves after drinking a glass of wine. Medications include L-thyroxine for hypothyroidism; family history + tremor
PE: 8 hz tremor with outstretched arms.

The best diagnosis is:
A. Parkinson disease
B. Essential tremor
C. Alcoholism
D. Normal aging
E. Manganese poisoning
Mr. Lem Quiver

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E. Manganese poisoning
Essential tremor

- Onset with aging
- Sometimes familial
- Head, voice, arms.
- Affects function (picking up coffee cup)
- Better one drink, worse many.
- Check thyroid function, meds.
- Rx betablockers, primidone.

Parkinson Disease

- Diagnosis of Parkinson Disease
  - Bradykinesia
  - At least 1 of: muscular rigidity, tremor, postural instability
  - 3 or more of: unilateral onset, persisting unilateral symptoms, rest tremor, ≥10 year course, progression over time, levodopa-induced chorea, levodopa response for ≥5 years
  - Exclude other neurologic disorders
Rx Parkinson Disease

- Treatment of Parkinson Disease
- Initial treatment, mild disease
  - MAO-B inhibitors: selegiline, rasagiline
  - Mid-level/Advanced (often used in combination)
    - Dopamine agonists: pergolide, ropinirole, pramipexole, bromocriptine +/- COMT inhibitors
    - Dopamine precursors: carbidopa/levodopa
- Hallucinations common side-effect
- Motor fluctuations are common; dopamine agonists can be helpful

Drug induced “parkinsonism”

- Anti-psychotics
- Pro-kinetic GI drugs – metoclopramide
- SSRIs, SNRIs
- Long term valproic acid
- Other disorders can appear “Parkinsonian”
  - progressive supranuclear palsy, multi-system atrophy, Lewy body disease
A 68-year-old woman with lung cancer (currently under treatment) is brought to your office with gradually increased confusion and walking difficulties. On exam, you find mild left-sided weakness and gait instability.

The most useful study to do first is:

- A. MRI with contrast
- B. EEG
- C. CBC, CMP
- D. EMG
- E. PET whole body
- F. Total insurance check

Ms. Bee Fuddle
Ms. Bee Fuddle

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Neuro-oncology

- Cancers with frequent CNS metastases:
  - Lung, breast, melanoma, lymphoma, leukemia
  - solid tumors go to brain
  - blood cancers go to meninges
  - Common presentations: headache, altered mental status, focal neurologic deficits
  - Resection of a solitary CNS metastasis can prolong life (even with systemic disease)
  - Treatment usually includes whole brain radiation
  - Biopsy is rarely necessary with known systemic cancer
  - Corticosteroids reduce edema
  - Gamma Knife radiosurgery can be effective
Neuro-oncology

- Primary CNS tumors
  - Meningiomas – common incidental CNS tumor
    - Often calcified, so frequently seen on head CT
    - Sometimes large size or location will lead to resection
  - Glial tumors
    - Most common primary brain tumor – 40%
    - Headache is common presenting symptoms
    - Seizures also common
    - Biopsy always required for grading, treatment plan, debulking
    - Most are high-grade, glioblastoma multiforme (GBM)
      - Treatment: temozolomide + XRT
  - Lymphomas
    - B-cell are most common, particularly with AIDS

Paraneoplastic syndromes

- Cerebellar degeneration, encephalomyelitis, sensory neuronopathy; myasthenic syndrome, opsoclonus (eye movement madness)
- Associated with a wide variety of systemic cancers, but particularly breast, small cell lung, and gynecologic
  - Specific antibodies can guide the search to targeted organs
- Neurologic symptoms almost always precede cancer diagnosis – only rarely do paraneoplastic syndromes develop after tumor is found
- Symptoms can improve if cancer is treated
- High dose corticosteroids and IVlg are effective when used early

Note recently publicized Ovarian teratoma associated encephalitis (NMDAR)
A 41-year-old man is brought into the emergency room with 30 minutes of continuous tonic-clonic movements in his arms and legs. Paramedics brought him from his lumber yard, where he was ripping boards. No other medical history is immediately available. He was intubated and a large-bore IV started during transit to your hospital. You diagnose status epilepticus.

- Which is the appropriate next step in your management?
  - a. 100 mg of thiamine IV
  - b. stat unenhanced head
  - c. lorazepam 0.1 mg/kg IV
  - d. 50 ml of 50% glucose (D50) IV
  - e. fosphenytoin 20mg/kg IV
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**Status Epilepticus**

- Management of status epilepticus
  - **Step 1:** ABCs, IV, stat labs
  - **Step 2:** thiamine, followed by glucose load
    - Thiamine prevents Wernicke’s syndrome
  - **Step 3:** Lorazepam 0.1 mg/kg, infused at <2 mg/min
    - Lorazepam is preferred over diazepam because its effect lasts longer
  - **STEP 4: CALL NEUROLOGY**

Step 1-3 at same time; speed of treatment is key in survival.
Mr. Will Dunk

A 28-year-old had a presumed cardiac arrest while playing pick-up basketball and suffered prolonged anoxia. 2 days after the event, he remains comatose. You believe he may be dead by neurological criteria.

Which of the following is the appropriate next step in declaring him dead by neurological criteria?

a. neurological evaluation
b. electroencephalogram
c. review the medical chart for medications and evidence of metabolic derangement
d. apnea test
e. perform transcranial doppler ultrasonography
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Death by brain criteria

- Brain death involves no activity of the cortex and brainstem.
  - Three cardinal signs: 1) coma, 2) no brainstem activity, and 3) apnea
- Death by neurological criteria starts with review of the medical chart, to ensure absence of homeostatic abnormalities
  - Confounding issues should be resolved before proceeding
- Neurological examination should include
  - Cranial nerve examination
  - Examination of reflexes and pain responses
- Apnea examination
  - No spontaneous respirations after 10 minutes and appropriate blood gases
- Ancillary tests:
  - Transcranial ultrasound, EEG, cerebral angiography, cerebral scintigraphy, CT angiography
  - Useful when unable to do a complete physical exam and/or apnea test, and what you were able to do was consistent with death by neurological criteria
Persistent coma after cardiac arrest

- Hypothermia treatment performed within 6 hours dramatically improves outcome. Please try to remember…

- Persistent vegetative state:
  - Definition: no purposeful responses to outside stimuli
  - No sensory processing; completely unaware of self
  - Often replaces coma after several weeks or months when brainstem function is preserved
  - Involves spontaneous eye openings, roving eye movements
  - Usually have sleep-wake cycles.
  - More than 3 months from event.
Case

A 47-year-old automotive mechanic presents with several months of numbness in his feet, with gradual spread to his calves. History is notable for diabetes and hypertension. He smokes 2 packs per day and drinks a few beers per night. You suspect a polyneuropathy.

All of the following are reasonable etiologies for his neuropathy except:

a. diabetes
b. smoking
b. smoking

c. alcohol
d. toxic exposure from his workplace
e. CIDP

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b. smoking

c. alcohol
d. toxic exposure from his workplace
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Neuropathies

- 2 classifications: focal (mononeuropathy) and generalized (polyneuropathy)
- 2 types: axonal, demyelinating
  - Axonal (involve nerve):
    - Diabetes mellitus and alcoholism are the most common
    - Other toxic insults: occupational; uremia
  - Demyelinating (involve surrounding myelin): usually autoimmune
    - Guillain Barré, chronic inflammatory demyelinating polyneuropathy (CIDP)
- Evaluation:
  - Fasting glucose, HGB A1c, BUN, creatinine, CBC, ESR, urinalysis, B12, SPEP (for gammopathy)
  - EMG NCS (identifies neuropathy, evaluates axonal/demyelinating/focal)
  - CSF studies when Guillain Barré is suspected
  - Nerve biopsy is rarely needed
- Treatment:
  - Axonal: removal of toxic agent; improve dysmetabolic state
  - Demyelination: immunosuppressants, pheresis, IVIG
  - Pain: gabapentin, tricyclics, duloxetine
Ms. Mia Algia

A 67-year-old woman is seen in your clinic for routine check-up and reports gradually increasing headaches for the past 4 months, which is unusual as she rarely gets more than a passing headache. Pain is bilateral and mild, but constant and throbbing. Her scalp is mildly tender. She’s involuntarily lost 10 pounds over the past six months, and has generalized muscle aches.

The most appropriate test is:

- a. EMG/nerve conduction study
- b. urgent unenhanced head CT
- c. brain MRI with and without gadolinium
- d. ESR and CRP
- e. GI consultation
Giant Cell (Temporal) Arteritis:
- Can cause irreversible visual loss (retinal ischemia)
- Headache is prominent – throbbing, generalized, persistent
- Polymyalgia rheumatica (50%) and jaw claudication (40%) are common (i.e. chewing tires during meals)
- Exclusively affects age >50 years
- Evaluation: requires emergent evaluation to prevent permanent visual loss
  ● Urgent erythrocyte sedimentation rate and C-reactive protein
  ● Corticosteroids (60 mg/d) should be started if GCA is considered likely
  ● Aspirin should probably also be given, unless contraindicated
- Diagnosis is confirmed by temporal artery biopsy
  ● If biopsy negative and suspicion high, biopsy opposite side
- Corticosteroids are usually needed for 1-2 years
  ● Monitor ESR and C-reactive protein
Lightning round

- 45 year old male has sudden worst headache of his life and within minutes lapses into a coma. He has a stiff neck, is breathing heavily, and has upgoing toes.

- Best diagnosis:
  - A. Viral Meningitis
  - B. Drug intoxication
  - C. Subarachnoid hemorrhage
  - D. Organophosphate poisoning
  - E. Belle indifference
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Lightning round

- 17 year old Lothario comes to the ED after spending 6 hours at the movies with his arm around his girlfriend’s shoulder. He has a wrist drop and can’t extend his fingers.

Best diagnosis:
- A. Ulnar nerve palsy
- B. Radial nerve palsy
- C. Median nerve palsy
- D. C5 radiculopathy
- E. Cord impingement
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Lightning round

- An 18 year old high school football player comes to you because try as he might he falls asleep in class. Sometimes when friends tell jokes his knees get weak. On occasion he feels paralyzed when going to sleep.

- Best diagnosis:
  - A. Conversion disorder
  - B. Temporal lobe epilepsy
  - C. Multiple Sclerosis
  - D. Narcolepsy
  - E. Steroid abuse

- D. Narcolepsy

Lightning round

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  - A. Conversion disorder
  - B. Temporal lobe epilepsy
  - C. Multiple Sclerosis
  - D. Narcolepsy
  - E. Steroid abuse
An alcoholic comes to the ED and is unsteady, has slurred speech, is confused, and has nystagmus. You give him something and 12 hours later he is much better.

What did you give him?
- A. Shot of tequila
- B. Shot of thiamine
- C. Shot of topamax
- D. Pot of coffee
- E. Lotta Naloxone
Lightning round

- A 23 year old female comes in with 2 day ascending tingling and weakness beginning in her legs and progressing to arms and face. She can’t walk. She has no reflexes and has 4 limb weakness, mild bifacial weakness. Labs are normal, CSF shows increased protein and normal cells.

- You start her on:
  - A. paper bag over the mouth
  - B. plasmapheresis
  - C. interferon beta 1a
  - D. gabapentin
  - E. steroids
Neurology: simple specialty

1. Is there a neurological problem?
2. Where in the nervous system is it?
3. What’s the etiology/pathogenesis/m Mechanism?