Willis' Morbisick Matter

Tuesday, March 2, 2017

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Case

- Chief complaint: Seizures
- You are seeing him in our ICU, he is awake
- History of Present Illness:
  - 24 year old man from Congo (immigrated ~10 months ago) with no past medical history was visiting his wife in a local hospital 2 days ago. She was pregnant and was hospitalized with pyelonephritis. With absolutely no prior illness in the preceding days or hours, the patient suddenly suffered a tonic-clonic seizure. He required intubation and both benzodiazepines and phenytoin to stop seizures (for status epilepticus) and was transferred to the local hospital's ICU.

Case, cont.

- Exam: 38.2 (100.8°F), P 129, R- 19, 136/91. O_2 saturation 99% on 0.4 FiO_2. Sedated. No apparent assessment of neck stiffness. Normal including lack of rash.
- Labs- (after resuscitation)
- WBC- 23,400, platelets- 110, Hemoglobin- 13.5, Hematocrit 47.8. (differential- 76.4% PMN, Lymphocytes- 11.7%, Monocytes 11.3%). Smear- clumped platelets
- Sodium- 143, Potassium- 3.9, Chloride- 111, CO2- 22, glucose- 112, BUN-10, Creatinine 1.0
- Liver tests: AST- 21, ALT- 21, Alkaline Phos- 71, Total protein- 7, Albumin- 3.5
- Sedimentation rate- 6, C-reactive protein 1.5 (normal 0-0.8). Procalcitonin- low
- Lactic acid- 2.4 mmol/L (normal). Ethanol- 0
- Urine drug screen- negative
- Chest xray was normal, Head CT- encephalomalacia in frontal lobes

Further tests?

Cerebrospinal fluid

- Opening pressure- 22 cm of water (10-18 normal)
- Cell count: 7 nucleated cells (0-5 /mm^3), 72% PMN, 26% lymphocytes.
- Total protein- 36 mg/dL (15-45)
- Glucose- 82 mg/dL (45-75); plasma was ~110 mg/dL
- Gram stain- no organisms seen
- MRI brain with contrast- normal except for bifrontal encephalomalacia with gliosis

Thoughts?

Case, cont.

- Started on acyclovir (anti-herpes simplex antiviral), vancomycin, ceftriaxone (3rd generation cephalosporin), ampicillin
- Malaria smear- negative
- No known family history of illness. The patient does not smoke, drink alcohol or used illicit drugs. Works at Tyson.
- Extubated the next day. Febrile, high as 40.4.
- Earlier today he became confused, and had another seizure.

CBC

Component Name	6/26/2015	6/25/2015	6/24/2015	6/24/2015
WBC	9.9	10.8	12.2 (H)	23.4 (H)
RBC	4.62	4.71	5.24	5.68
Hemoglobin	11 (L)	11.4 (L)	12.6 (L)	13.5
Hematocrit	34.8 (L)	35.2 (L)	40.3	47.8
MCV	75.3 (L)	74.7 (L)	76.9 (L)	84.2
MCH	23.8 (L)	24.2 (L)	24 (L)	23.8 (L)
MCHC	31.6 (L)	32.4	31.3 (L)	28.2 (L)
Platelets	184	152	200	110 (L)
RDW	15.4 (H)	15.5 (H)	15.3 (H)	14.9 (H)
Platelet Estimate				DECREASED

CHEM PROFILE

Component Name	6/26/2015	6/26/2015	6/25/2015	6/25/2015
Sodium	142	142	141	144
Potassium	3.4 (L)	3.5	3.7	4
Chloride	107	107	109 (H)	114 (H)
CO2	27	28	24	20 (L)
Glucose	110 (H)	107 (H)	111 (H)	98
BUN, Blood	8	8	10	11
Creatinine, Serum	0.78	0.79	0.94	0.99
Total Bilirubin		0.3		0.5
AST		1019 (H)		301 (H)
ALT		247 (H)		68
Alkaline Phosphatase		55		57
Total Protein		5.5 (L)		6.5
Albumin		2.8 (L)		3.1 (L)
Calcium	7.8 (L)	7.9 (L)	8.8	8.6

HIV-neg

Thoughts?

CSF #2

SPINAL FLUID

Component Name	6/26/2015	6/26/2015	6/24/2015
Color, CSF		COLORLESS	COLORLESS
Appearance, CSF		CLEAR	CLEAR
WBC, CSF		905 (H)	7 (H)
RBC, CSF		78 (H)	46 (H)
Polys %, CSF		74	72
Lymphs %, CSF		26	26
Mono/Macrophage, CSF %		0	2
Comment, CSF		TUBE 2	TUBE 1
Protein Total, CSF		95 (H)	36
Glucose, CSF		60	82 (H)
Other Cells, CSF		0	
S Pneumo Ag, CSF	NEG		
GPB Strep Ag, CSF	NEG		
H Influenza, CSF	NEG		
N Meningiditis C/W Ag, CSF	NEG		
N Meningiditis A/Y Ag, CSF	NEG		
N Meningiditis Ec K1, CSF	NEG		

Patient transferred to UIHC

- You get a call from the local laboratory

Culture result

- *Neisseria meningitidis*
- MICs
- PCN 0.5 μg/ml (susc is ≤ 0.06 μg/ml, < 0.1)
- Ceftriaxone- < 0.016 μg/ml (≤ 0.12)
- Meropenem- 0.032 μg/ml (≤ 0.25)
- He got 9 days total ceftriaxone

Discussion

- Definition and history of meningitis
- Brief discussion of epidemiology
- Question for Kayley
- Clinical feature of interest:
  - Remarkably quick onset of illness prior to inflammation (seizure with no prior malaise)

Meningitis

- Inflammation of the meninges
  - Identified as elevated white blood cell count in the cerebrospinal fluid
- Acute and chronic
  - Chronic (≥4 weeks symptoms and signs)
- Contrast with encephalitis
  - Meningitis: fever, headache, meningeal irritation ± altered mental status
  - Encephalitis: fever, altered mental status, headache

Etiologies

Aseptic- viral

Bacteria
Haemophilus influenzae
Neisseria meningitidis
Streptococcus pneumoniae
Listeria monocytogenes
Escherichia coli
Streptococcus agalactiae

TABLE 89-1 Differential Diagnosis of Acute Meningitis

Major Infectious Causes
Viruses
Nonpolio enteroviruses[a]
Arboviruses[b]
Herpesviruses[c]
Lymphocytic choriomeningitis virus
Human immunodeficiency virus
Adenovirus
Parainfluenza virus types 2 and 3
Rickettsiae
Rickettsia rickettsii
Rickettsia conorii
Rickettsia prowazekii
Rickettsia typhi
Orientia tsutsugamushi
Ehrlichia and *Anaplasma* spp.
Bacteria
Haemophilus influenzae
Neisseria meningitidis
Streptococcus pneumoniae
Listeria monocytogenes
Escherichia coli
Streptococcus agalactiae
Propionibacterium acnes
Staphylococcus aureus
Staphylococcus epidermidis
Enterococcus spp.
Klebsiella pneumoniae
Pseudomonas aeruginosa
Salmonella spp.
Acinetobacter spp.
Viridans streptococci (e.g., *S. salivarius*)
Streptococcus gallolyticus
Fusobacterium necrophorum
Stenotrophomonas maltophilia
Streptococcus pyogenes
Streptococcus suis
Pasteurella multocida
Capnocytophaga canimorsus
Nocardia spp.
Mycobacterium tuberculosis
Spirochetes
Treponema pallidum (syphilis)
Borrelia burgdorferi (Lyme disease)
Borrelia miyamotoi
Leptospira spp.

Protozoa and Helminths
Naegleria fowleri
Angiostrongylus cantonensis
Baylisascaris procyonis
Taenia solium
Toxocara spp.
Strongyloides stercoralis (hyperinfection syndrome)
Other Infectious Syndromes
Parameningeal foci of infection[d]
Infective endocarditis
Viral postinfectious syndromes
Postvaccination[e]
Noninfectious Causes and Diseases of Unknown Etiology
Intracranial Tumors and Cysts
Craniopharyngioma
Dermoid/epidermoid cyst
Teratoma
Medications
Antimicrobial agents[f]
Nonsteroidal anti-inflammatory agents[g]
Muromonab-CD3 (OKT3)
Azathioprine
Cytarabine (high dose)
Carbamazepine[h]
Immune globulin
Ranitidine
Phenazopyridine
Systemic Illnesses
Systemic lupus erythematosus
Behçet's disease
Sarcoidosis
Vogt-Koyanagi-Harada syndrome
Procedure-Related
After neurosurgery
Spinal anesthesia
Intrathecal injections[i]
Chymopapain injection
Miscellaneous
Seizures
Migraine or migraine-like syndromes

CSF analysis

- Clinical challenge is identifying viral versus bacterial given fact that CSF culture is not 100% sensitive
- Some findings suggest bacterial cause
  - >2,000 WBC, >80% PMNs, glucose < 4 mg/ml (ratio to serum < 0.4), protein > 200 mg/dL
- Exceptions exist (like our patient)

Etiologies for acute bacterial meningitis

Predisposing factor	Common bacterial pathogens
Age	
<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* species
1–23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*
2–50 years	*N . meningitidis, S. pneumoniae*
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli
Head trauma	
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A β-hemolytic streptococci
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci (especially *Staphylococcus epidermidis),* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa)*
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa), S . aureus,* coagulase-negative staphylococci (especially *S. epidermidis)*
CSF shunt	Coagulase-negative staphylococci (especially *S. epidermidis), S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa), Propionibacterium acnes*

History

- Described syndromes called “phrenitis” and “cephalitis.” Seem to match patients we would now diagnose with meningitis or encephalitis
- The English physician, Dr. Thomas Willis (1621–1675):
  - “The Phrensy is defin’d: That it is a continual raving, or a depravation of the chief faculties of the brain, arising from an inflammation of the meninges with a continual fever.”
  - Ancient term is source of current “frenzy”

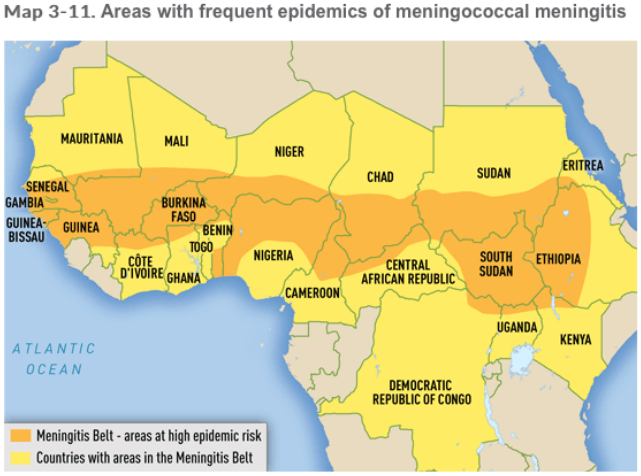
“Every Man knows that Convulsions sometimes happen to Persons in Fevers, and from thence a very great Prognostick is taken of death or danger...a Vertigo or Delirium arise from the Morbisick Matter’s being depos’d from the Blood in the Brain . . .”

History, cont.

- Dr. Robert Whitt (1714-1766) described the clinical syndrome most clearly
- Dr. John Cheyne (1777–1836):
  - Acute hydrocephalus- “the ventricles of the brain are found enlarged and full of lymph”
  - Refined definitions to distinguish acute from chronic
- Several Swiss physicians described epidemics of meningitis in Geneva
  - Noted purpuric lesions

Neisseria meningitidis

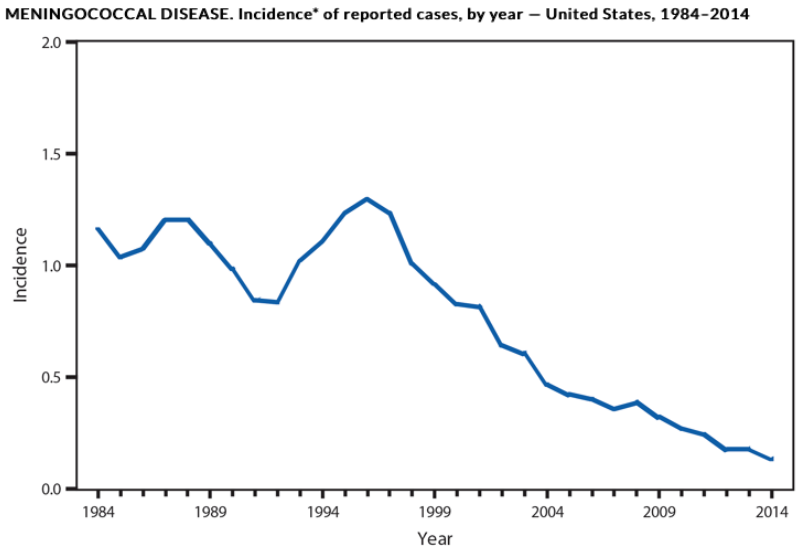
- Second most common cause of bacterial meningitis in US
  - Mortality 11% in US
- Colonization precedes disease
- Endemic disease- sporadic
- Epidemic disease- organism can colonize a large # in a short time
- Serotypes: A,B,C, W, Y135 most common
  - Vaccine for A,C Y, W135 recommended routinely
  - Vaccine for type B for some patients



"meningitis belt"

US Epidemiology

- Overall US incidence .52 per 100,000 per year
- Highest in infants < 1 y (5.4 cases per 100,000 per year)
- Serogroups C, Y, and B are most frequent
- Recent outbreaks in men who have sex with men



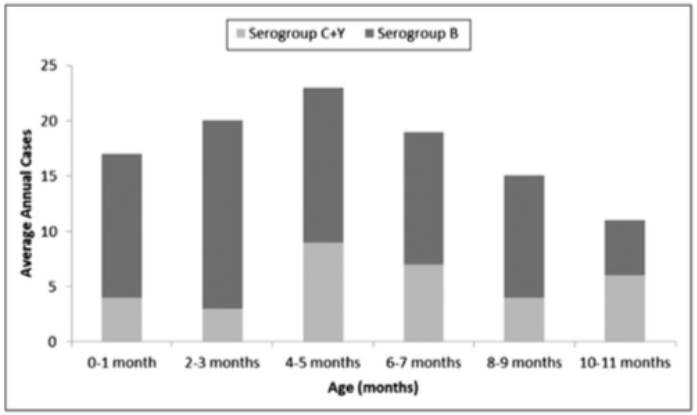


FIGURE 1
Average annual cases of meningococcal disease by month of life and serogroup, United States, 2006–2012. ABCs cases from 2006 to 2012 are directly standardized to the race distribution of the US population.

Question for Kayley

- Relatively few bacteria cause community-onset meningitis
  - *S. pneumoniae, N. meningitidis*, *L. monocytogenes*
  - *Streptococcus agalactiae* and *E. coli*
  - *Klebsiella pneumoniae* (hypermucoviscous strains)
- Why is *Neisseria meningitidis* so good at entering the CSF and causing meningitis?