A Pathologist’s Perspective on Naegleria Fowleri Meningoencephalitis (PAM)

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PAM was diagnosed in only 27% of patients before death.

Are there opportunities to improve the yield of the present diagnostic process?
Diagnostic Process

• Clinical
• Laboratory
Clinical Diagnostic Process

• Through history and physical examination define a category of diseases
• Design a strategy to sort the diagnostic possibilities
History

- Water Exposure – sensitive but non-specific
- Nature of the water exposure – helpful in some cases
28% of PAM Patients Presented with Flu like Symptoms

- Headache
- Nausea/vomiting
- Fever
- Fatigue
- Earache

In the United States, about 4,100 cases of bacterial meningitis, including 500 deaths, occurred each year between 2003–2007.

In 2005 there were approximately 40,000 hospitalizations for viral meningitis in the US.

From 1937 to 2013, 142 patients with PAM were reported in the United States.

CSF Laboratory Findings to the Clinician

- Cell count & differential
- Glucose & Protein
- Gram stain
CSF Finding in PAM

• Cell count and differential 2400/µL (range 5 – 26,000), 83% neutrophils (range 21% – 98%)
• Protein – 365 mg/dL (range 24 – 1210)
• Glucose – 23 mg/dL (range 1 – 92)
• The above values are similar to those usually found in bacterial meningitis
• Antibiotics were used in 94% of patients
Concentration of Naegleria fowleri in a given CSF Sample

- Not known with certainty
- 38 of 39 antemortem identifications were by hematocytometer (Capewell LG et al)
- Case report with CSF findings of 310 RBCs and 300 WBCs with 83% neutrophils
- Hematocytometer - 118 motile amoeba/mm³

DOI: 10.1056/NEJM196912112812401
Detection of amoeba by motile cells in CSF

- Capewell et al - only 47 patients had cell count data.
- Motility is commonly seen in body fluid specimens – ciliated respiratory epithelium in pulmonary lavage fluid so technologists should recognize it.
- May not be seen because motile organisms are few in number or the organisms lose motility for a variety of reasons.
Detection of amoeba by motile cells in CSF

• 18 year old Orlando high school student
• Initial CSF- WBCs – 20,000/mm3, 88% neutrophils, motility not observed
• Twelve hours later CSF – WBCs 15,200/mm3. After “...warming with a hot penny...active directional amebas were seen.”

Detection of Amoeba by Wright Stain

- Case report with csf findings of 310 RBCs and 300 WBCs with 83 % neutrophils
- Wright stain - 10 amoeba/100 WBCs*
- Recall the average csf cell count data was 2400/µL(range 5 – 26,000), 83% neutrophils (range 21% - 98%)(Capewell LG et al)
- The above implies most specimens with csf neutrophilic pleocytosis should have amoeba visible on the Wright stained slides

DOI:10.1056/NEJM196912112812401
Why not seen on Wright stained slide?

- Outnumbered by inflammatory cells.
- Superficial resemblance to inflammatory cells
- Neutrophilic pleocytosis associated with a more common diagnosis
- Slides are discarded after 7 days
Lab section visited for problematic bacterial meningitis cases

• Microbiology
• Gram stain may or not be reviewed.
• Organisms seldom seen on gram stain.
• Wright stain slide in hematology section is generally seen by the hematology technologist only
PAM & CSF Pleocytosis

- May not be neutrophilic
- One of three cases in the initial US description PAM was a 10 year old boy who presented with mild nuchal rigidity, occasional vomiting and low grade fever – WBCs – less than 5/mm3 and glucose, 70 mg/dL. 24 hours later repeat LP showed 27,000/mm3 with 73% neutrophils. Motile amoeba were identified.

PAM & CSF Pleocytosis

- 8 year old male presented with frontal headaches, nausea, fever and vomiting

- Admission CSF – 17 RBCs/µL, 19WBCs/µL with 74% PMNs

- Died three days after admission – diagnosis made at autopsy

Stephany JD, Pearl GS, Gonzalez O. Arch Pathol Lab Med, 2004; 128:e33-e34.
A seven year old female is admitted to Children’s, with probable bacterial meningitis...
History

• Well until two days prior to admission.
• Complained of headaches and neck pain.
• Developed fever to 39.2°C.
• Seen at an urgent care clinic the day before admission and is reported to have had a positive rapid strep test.
History

- Received an IM dose of penicillin at urgent care clinic and was discharged home.
- Over the subsequent 12 hours her condition deteriorated, she became unresponsive to her parents and was brought to the Children's ER.
CT Scan

• "Normal brain parenchyma. Normal size and configuration of the ventricles.

• Normal size and symmetry of suprasellar cistern and basilar cistern, no evidence of midline shift, or mass effect.

• No evidence of intraparenchymal or intraventricular bleeding..."
CSF

- 8150 WBC's/uL (normal range 0 - 10).
- CSF cell count - 90 percent neutrophils, 4 percent lymphocytes and 6 percent monocytes.
- Glucose - less than 6 (40 - 70) mg/dL.
- Protein - 461 (15 - 40) mg/dL.
- Gram stain - 4+ WBC's; no organisms.
Presumptive diagnosis: bacterial meningitis

- Cefotaxime 1.5 gm IV q6h.
- Vancomycin 600 mg IV q6h.
- Possibly due to Streptococcus pyogens (positive rapid Strep test in physician’s office)
Further History

• Very involved in gymnastics class.
• History of swimming in area waters.
• No pets or animal exposures besides at county fair several weeks earlier.
• Deer tick exposures earlier in summer.
• No history of travel outside Minnesota - Wisconsin.
Day 2 Study Results

- CSF latex antigen studies for H influenzae and N. meningitidis – negative.
- CSF bacterial culture - negative
Day 3

- Dilated pupils; No pupillary reflex obtained bilaterally.
- No gag reflex present
- No corneal reflex present. No reaction to painful stimuli.
- No spontaneous movement.
- Gram stain reviewed afternoon of day 3 and negative
- Death at 2330 hours, day 3.
What do we know about Group A Streptococcus Meningitis?
## Invasive Group A Streptococcal Disease

<table>
<thead>
<tr>
<th>Category</th>
<th>Cases (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia without focus</td>
<td>147(22%)</td>
</tr>
<tr>
<td>Skin or soft tissue</td>
<td>196(30)</td>
</tr>
<tr>
<td>Necrotizing fasciitis</td>
<td>104(16)</td>
</tr>
<tr>
<td>Pleuropulmonary</td>
<td>71(11)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>32(5)</td>
</tr>
<tr>
<td>Intra-abdominal</td>
<td>24(4)</td>
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<tr>
<td>Septic arthritis</td>
<td>59(9)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>22(3)</td>
</tr>
<tr>
<td>Other</td>
<td>48(7)</td>
</tr>
</tbody>
</table>

J Clin Microbiol, 2011;49(12):4094 -4100
“Group A streptococcus is an uncommon cause of meningitis in children. We report a single case of Group A streptococcus meningitis, in an apparently healthy 6-week-old infant. Twenty-five cases in the English-language literature in the last 25 years and our case are reviewed...”

Prior to Autopsy

- Reviewed Gram stain on last day of life – no organisms seen. Wright stain not sent with gram stain
- Day of autopsy – reviewed history; examination of gross anatomy
- Obtained Wright-Giemsa stained slide of CSF from admission
Wright Stained CSF
Area Adjacent to the optic chiasm
Microabscess, right caudate/putamen nuclei
Naegleria Meningoencephalitis

• “...trophozoites proved to be difficult to identify on initial review of hematoxylin and eosin stained slides because of intense infiltrates by macrophages or the presence of necrotic debris...”
Diagnostic Modalities

- PCR
- Immunohistochemistry (CDC)
- Serology
- Light Microscopy
Fatal Naegleria fowleri infection acquired in Minnesota: possible expanded range of a deadly thermophilic organism.

Points to Remember

- CSF neutrophilic pleocytosis without a positive gram stain should prompt review of the Wright Giemsa stained CSF slide to rule out PAM.
- In cases of CSF neutrophilic pleocytosis with a negative gram stain and no significant medical history, detailed history of freshwater exposures should be obtained.
- Neutrophilic pleocytosis does not define all presentations of PAM.
- Naegleria are not usually seen on gram stains.
A rare parasite in the water

A total of 132 cases of primary amebic meningoencephalitis caused by N. fowleri were reported in the United States from 1962 through 2014, including 35 since 2005.

Source: Centers for Disease Control and Prevention

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Freshwater Swimming Areas
Area Adjacent to the optic chiasm