

# Primary Amoebic Meningoencephalitis (PAM)

## Background

1. Definition: rapidly progressive meningoencephalitis caused by free-living amoeba, *Naegleria fowleri*.
2. General Information:
  - Recognized distribution world-wide.
  - Most frequently occurs in otherwise healthy children or young adults.
  - Associated with recent exposure to warm freshwater environments, such as lakes, ponds, canals, puddles, and under-chlorinated pools.

## Pathophysiology

1. Pathology:
  - Free living amoeba transmitted intranasally by inhalation of contaminated dust or more commonly, contaminated water.
  - Amoeba suffuse the nasal mucosa, traveling along the olfactory nerves, and access the CNS via the olfactory bulbs.
  - Directly damage brain parenchyma, ependyma, and meninges and incur an extensive inflammatory response, inciting a rapidly progressive meningoencephalitis.
  - Autopsy findings demonstrate swollen, edematous cerebral hemispheres with diffuse superficial cortical hemorrhages and hyperemic meninges with purulent exudates.
    - The olfactory bulbs demonstrate considerable purulence, necrosis and hemorrhage.
  - Focal demyelination has been observed in white matter devoid of active infection, concerning for presence of lytic-like enzyme diffusing from adjacent infected gray matter.<sup>11</sup>
  - Case reports of associated myocarditis raise suspicions of possible circulating myotoxin.<sup>11</sup>
2. Incidence/Prevalence: Extremely rare.
  - Occurrence of infection estimated at 1 per 2.6 million exposures<sup>11</sup>
  - First reported in 1965 in Australia.
  - Global incidence, with a tendency toward warmer climates.
  - Since 1962, 111 cases reported in US, more than half of the cases reported in Florida and Texas.<sup>14</sup>
3. Risk Factors
  - Most cases were preceded by exposure to warm, freshwater environments, including ponds, lakes, canals, puddles, and swimming pools.
  - Predominantly affects males (79.3% of reported US cases).<sup>14</sup>
  - Peak age group 10-14 years old.<sup>14</sup>
  - Concerns over forceful propulsion of water into nose.
  - Most cases documented following exposure in July, August.<sup>14</sup>
4. Morbidity/Mortality: Nearly always fatal.
  - Mortality greater than 95%.
  - Mean time from exposure to death, 10 days (range 6-17 days).

## Diagnosics

1. PAM mimics other meningoencephalitic infections. A high index of suspicion is required for prompt diagnosis.
2. History: Presentation similar to fulminant bacterial meningitis or viral meningitis.
  - Acute onset bilateral frontal headache refractory to analgesia
  - Anorexia with associated nausea/vomiting
  - Fever, ranging 38.0-41.0C
  - May complain of loss of taste/smell.
  - Altered mental status
  - Seizures and lethargy common
  - May report recent history of exposure to contaminated water source.
    - Incubation period between exposure and onset of symptoms: 2-15 days.
3. Physical Examination:
  - Nuchal rigidity
  - Cerebellar ataxia
  - Cranial nerve palsies common, particularly III, IV, and VI.
    - III nerve palsy could indicate uncal herniation.
4. Diagnostic Testing:
  - Hematology/Chemistry
    - Elevated leukocytes
    - Hyperglycemia
    - Glycosuria
  - CSF profile similar to bacterial meningitis:
    - Elevated CSF protein
    - Normal or decreased CSF glucose
    - Marked pleocytosis, predominantly PMNs
    - Negative CSF bacterial cultures
  - CSF Microscopy:
    - Gram staining not effective for visualizing *Naegleria*
    - Wright stain, Giemsa stain have better utility
    - Wet mount of spinal fluid will demonstrate motile flagellate amoeba or trophozoites
      - Unrefrigerated CSF, examined within 30 minutes of collection is best.
      - Can be difficult to differentiate between macrophages and trophozoites.
    - Definitive diagnosis can only be made by culturing the amoeba on non-nutrient agar plated with *E. coli* or by specific monoclonal immunofluorescent staining.
  - Imaging: CT/MRI may be normal.
    - Signs of increased ICP: diminished sub-arachnoid space, uncal and cerebellar tonsil herniation are common.
    - Meningeal enhancement, consistent with other meningitides.
    - Late findings: severe cerebral edema, herniation

## Differential Diagnosis

1. Bacterial Meningitis
2. Viral Meningitis
3. Fungal Meningitis
4. Granulomatous Amebic Encephalitis
5. Complicated Migraine
6. Toxin mediated encephalopathy
7. Lyme disease
8. Brain Abscess
9. CNS Malignancy

## Therapeutics

Due to the rarity of PAM cases, and relative lethality of the illness, there is limited data available to determine effective treatment. Treatment recommendations are derived from in vitro experimentation and anecdotal cases reports.

1. Amphotericin B
  - Considered mainstay of treatment
  - All reported survivors treated with AMB at anti-fungal dosing
  - Intravenous administration can be coupled with intrathecal administration
    - IV: 0.75mg-1.5mg/kg/day
    - Intra-theical: 0.1mg-1.5mg/day
2. Rifampin
  - Reported synergy with Amphotericin in vitro<sup>5</sup>
  - Documented component in some successful treatment cases<sup>10, 12, 13</sup>
  - Administered orally:
    - 10mg/kg q 12 hours, up to 600mg q 12 hours
3. Azithromycin
  - Demonstrated efficacy in vitro<sup>8</sup>
4. Minocycline
  - Demonstrated limited efficacy in vitro.<sup>9</sup>
5. Dalfopristin/Quinupristin
  - Demonstrated efficacy in vitro<sup>9</sup>
6. Dexamethasone
  - Cochrane review showed efficacy in reducing neurologic impairment from bacterial meningitis, no clear mortality benefit.<sup>4</sup>
  - Documented component in some successful treatment cases<sup>10</sup>

## Follow-up

1. Admission
  - Patients with suspected meningitis should be admitted for evaluation.
2. Referral
  - Consider referral to tertiary care facility for patients with signs and symptoms of fulminant meningitis with negative Gram stain and cultures of CSF.

## Prognosis

1. Poor prognosis, generally fatal
  - Progression from onset of symptoms to death in 3-7 days.
  - Few survivors reported in literature
  - Importance of early detection and treatment

## Prevention

1. Exposure
  - Warm freshwater
    - Avoid stagnant lakes, ponds, canals, under-chlorinated pools
    - Swimming, total immersion, splashing, diving, etc..
  - Prevalence in warm weather months
    - July, August case reports predominate in US<sup>14</sup>
  - Geographic distribution
    - Warmer climates predominate in case reports.

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