Amoebic Meningoencephalitis: Etiology, Infection and Prevention

Jafar Ahmed, Nazeer Hyder, Christopher Meusburger, Nicole Rosteski, Nicole Sottile, & Tyler Welch

Faculty: Subhajit Dasgupta PhD and Hareesh Gugnani PhD

Medical Case Study

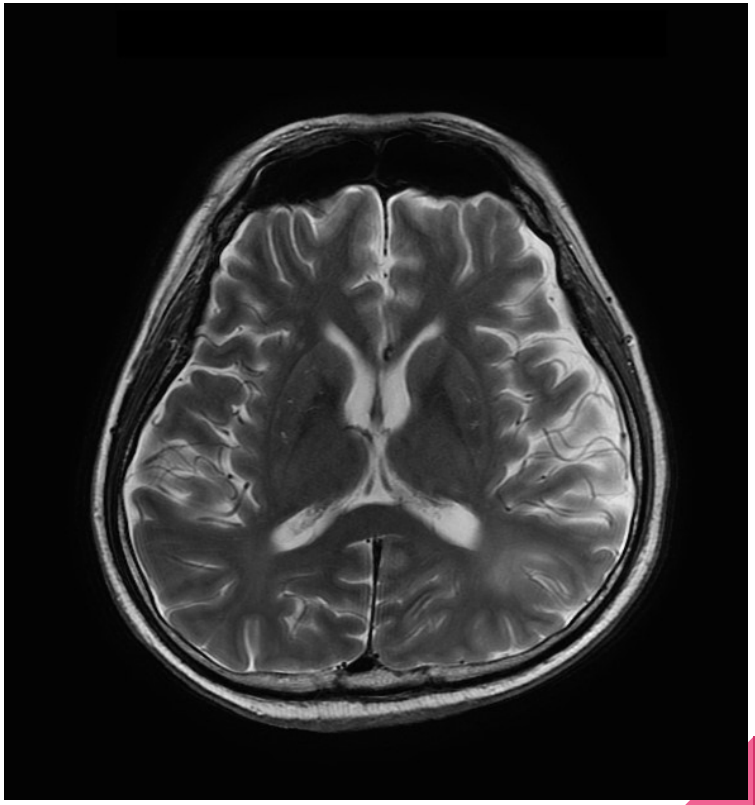
A 15 year old male is brought in by his mother to the clinic and presents with severe headache, nausea, a stiff neck, signs of delirium and vomiting. He has a body temperature of 39.3°C (102.7°F), pulse rate of 96, respiratory rate of 24 breaths per minute and a blood pressure of 140/92mm Hg. His mother informs you that her son was perfectly fine a week ago. About three days prior however, their entire family had spent the hot summer day at the lake. To confirm your suspicions you order a CSF test that indicates the presence of *Naegleria fowleri* organism., you begin treatment by administering Miltefosine and Voriconazole with ice bags packed around the patient.

CSF serum Results:

Test	Result	Normal
Red Blood Cells	25000/mm^3	4.52-5.90 x10^3/mm^3
White Blood Cells	22000/mm^3	4500-1000/mm^3
Glucose	10mg/100 mL	140mg/mL

MRI

The patient’s MRI was obtained and diffuse encephalitis can be seen



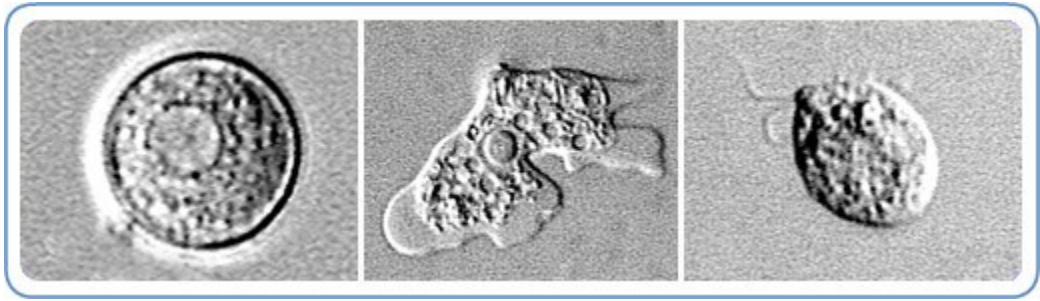
Primary Amoebic Meningoencephalitis

Naegleria fowleri

Free living microscopic ameba

Primary cause of Amoebic meningoencephalitis

Most commonly found in fresh and warm water of lakes, rivers and springs



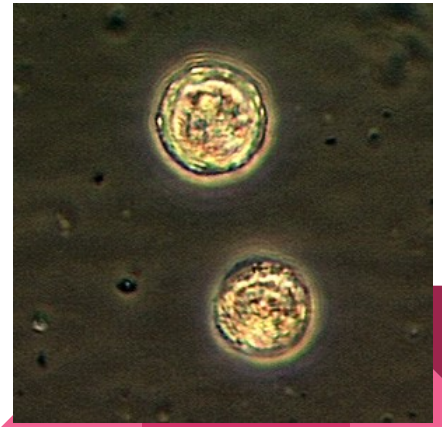
Amoebic Meningoencephalitis

Acanthamoeba Species

- Microscopic free living ameba responsible for:
  - Acanthamoeba keratitis
  - Granulomatous Encephalitis
  - Disseminated infection
- Found in bodies of fresh water

Balamuthia mandrillasis

- Free living ameba found in soil, spread through contact of open wounds



Pathogenesis

<u>Etiological agent of PAM - Naegleria fowleri</u>

Free-living organisms with no human carrier states

Rapid onset of infection and ultimately death

<u>Penetration of olfactory mucosa</u>

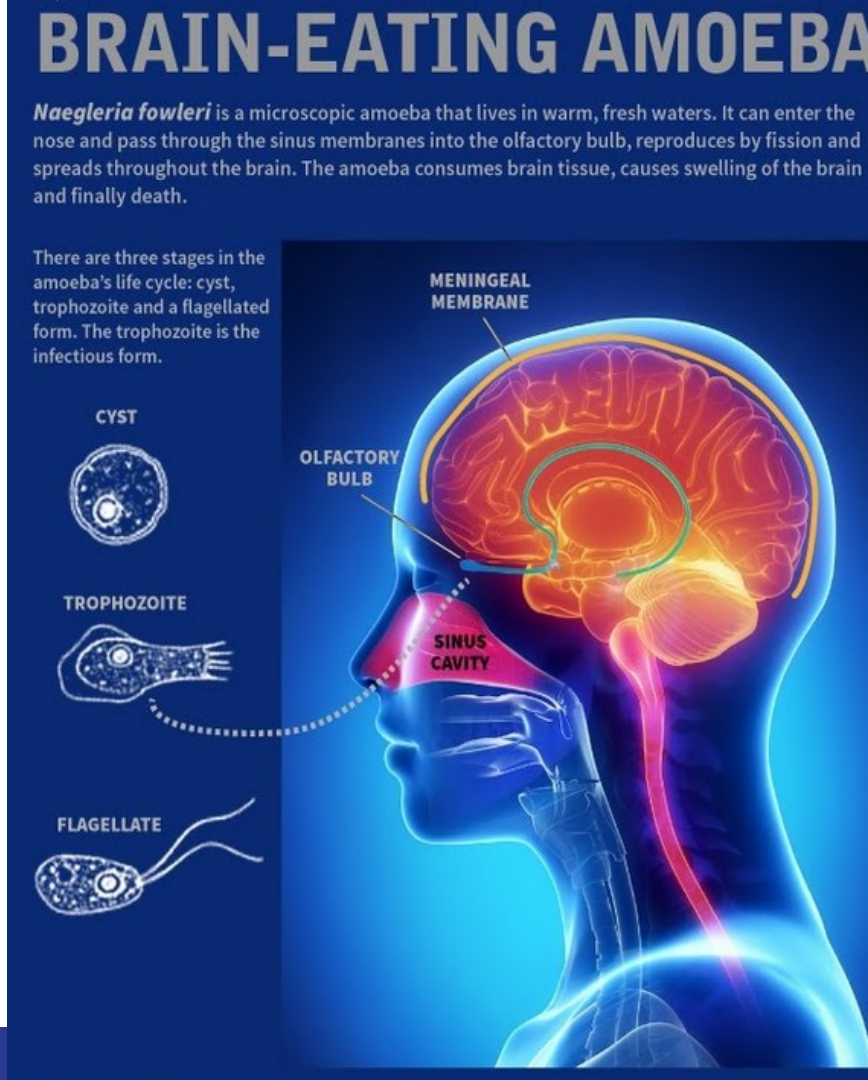
Mucinolytic protein Nfa1 degradation and cytolysis

Cribriform plate invasion permitting subarachnoid space entry

CSF nutrients and high cerebral O2 content facilitates growth

Choroid plexus entry through Foramen of Luschka & Magendie

Trophozoites exhibit promitotic multiplication and form lesions



Pathogenesis

<u>Etiological agents of GAE -</u>

Acanthamoeba species and *Balamuthia mandrillaris*

Subacute presentation

Highly associated with immunocompromised patients

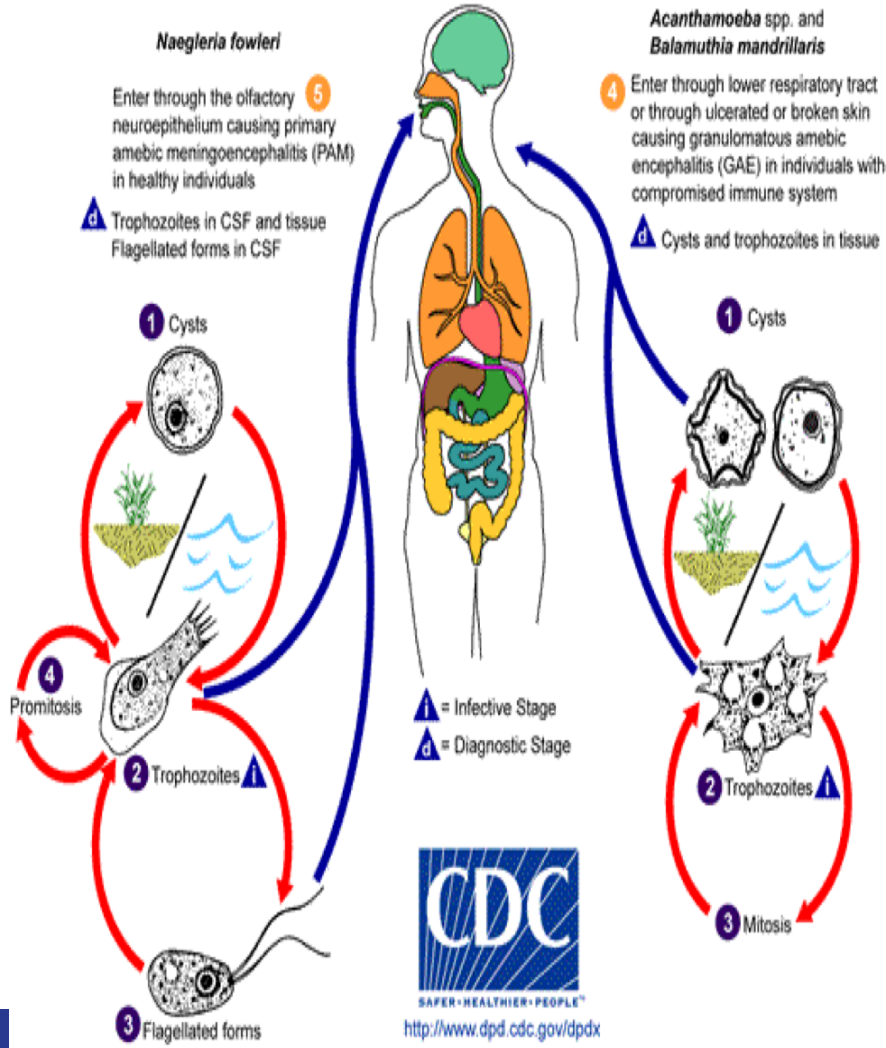
Inflammatory necrosis of brain tissue via amoebic infiltration

<u>CNS access:</u>

MC hematogenously via the respiratory tract or broken skin

1 ° inoculation sites and focal granulomas in the lungs & skin

Olfactory entry via acanthamoeba keratoconjunctivitis



Transmission PAM

- Contaminated water with *Naegleria fowleri* via nose
    - Most commonly swimming or rinsing sinuses with neti pot
        - NOT FROM DRINKING, NOT FROM PERSON-PERSON CONTACT

- Transmission path: Nose → optic nerve → brain

Transmission of GAE

-*Acanthamoeba* can enter via the eye with poor contact lens hygiene, or wearing contacts during swimming or hot tub use → cause infection of the cornea

-Also through the skin via cut/wound → blood → other parts of body

-*Balamuthia mandrillaris* → respiratory tract or through cut or ulcerated skin

Not transmitted from patient to patient

HIV/Immunocompromised/transplant patients

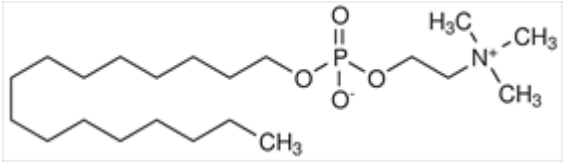
Signs and Symptoms of PAM

- Start within 1 to 9 days
- 2 Stages
- Death within 1- 18 days after symptoms begin
- Stage 1 (early infection)
    - Severe frontal headache, fever, nausea, vomiting, taste and smell change
- Stage 2 (late infection)
    - Stiff neck, seizures, altered mental status, hallucinations, coma

Signs and Symptoms of GAE

- Mental status change
- loss of coordination fever, muscular weakness, double vision, photophobia, or other neurological problems

Treatment



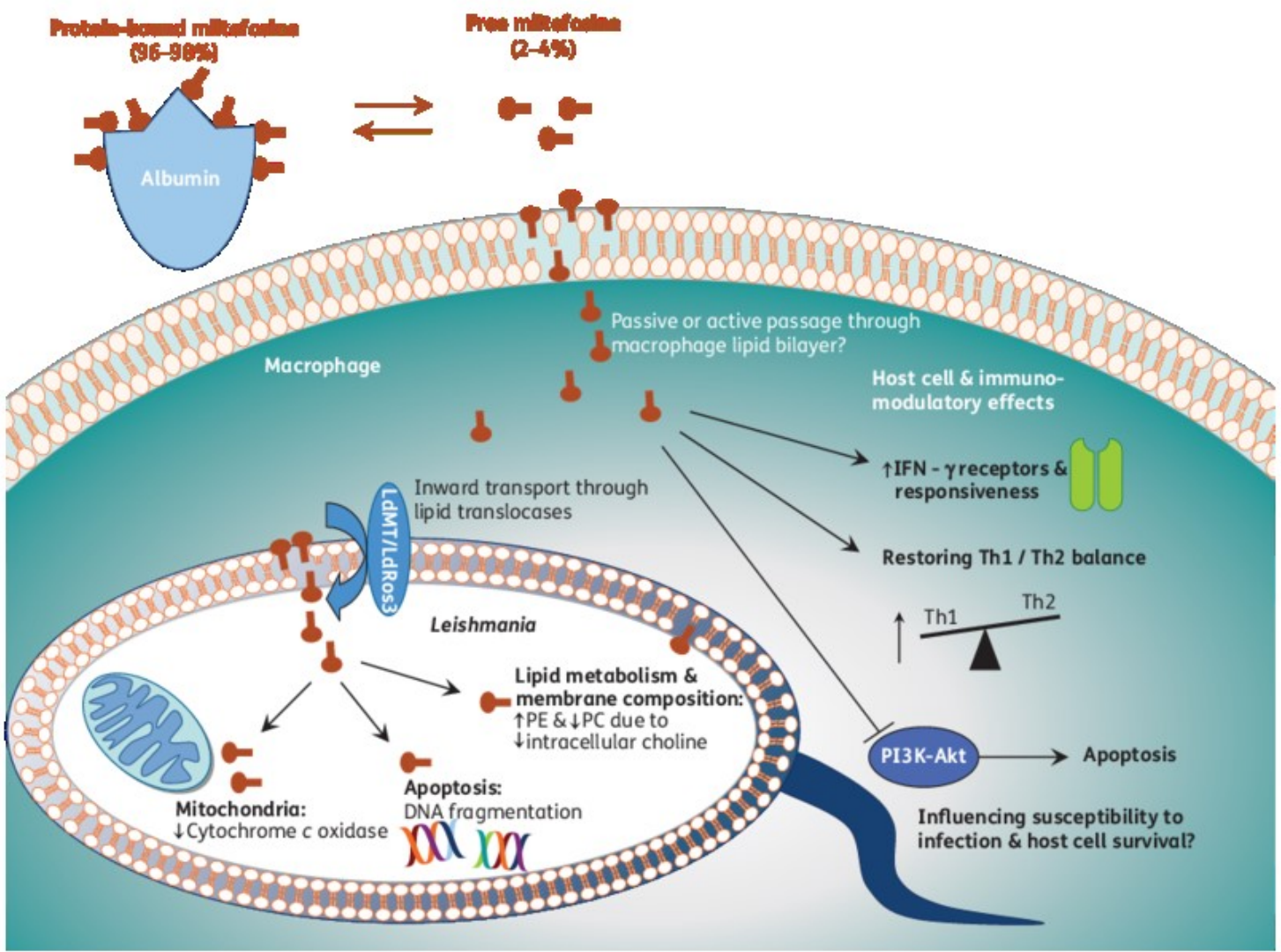
Miltefosine - anti-leishmania

Successfully treats *Balamuthia* and disseminated *Acanthamoeba* infections.

Mix with Voriconazole and hypothermia for best results

Four survivors, one is arbitrary (PAM)

Prior treatment:amphotericin B, at maximally tolerated doses, with adjunctive rifampin and doxycycline and ceftriaxone.


Protein-bound miltefosine
(96–98%)
Free miltefosine
(2–4%)
Albumin
Macrophage
Passive or active passage through
macrophage lipid bilayer?
Host cell & immuno-
modulatory effects
↑IFN - γ receptors &
responsiveness
Restoring Th1 / Th2 balance
Th1
Th2
Inward transport through
lipid translocases
LdMT/LdRos3
Leishmania
Lipid metabolism &
membrane composition:
↑PE & ↓PC due to
↓intracellular choline
PI3K-Akt
Apoptosis
Mitochondria:
↓Cytochrome c oxidase
Apoptosis:
DNA fragmentation
Influencing susceptibility to
infection & host cell survival?

Prevention

Knowledge and information

Avoidance of potentially infested waters

When potential exists utilize nose plugs

In swimming pools, ensure adequate chlorination

Epidemiology: Endemic Regions

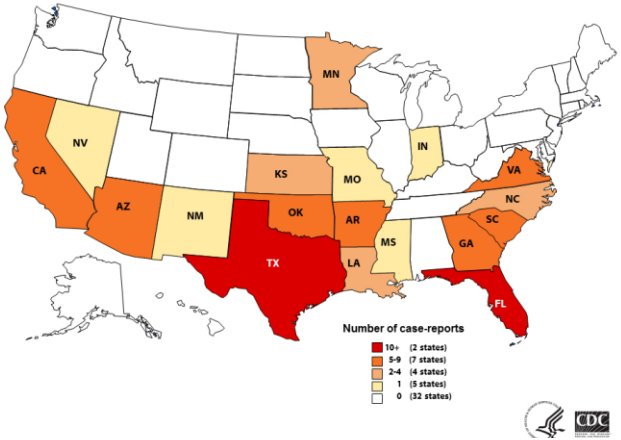
Global

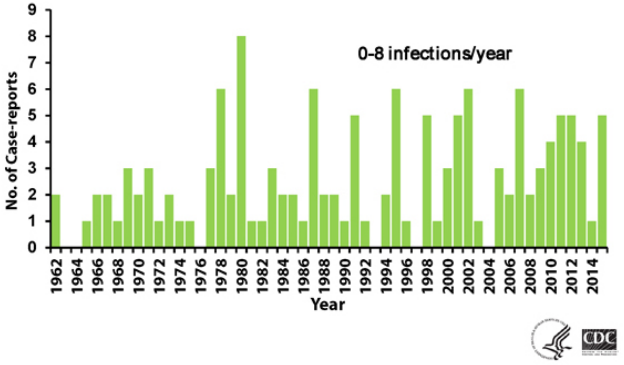
- PAM and GAE reports from US, Australia and Europe
  - Reporting Bias
- *Balamuthia* South America

United States

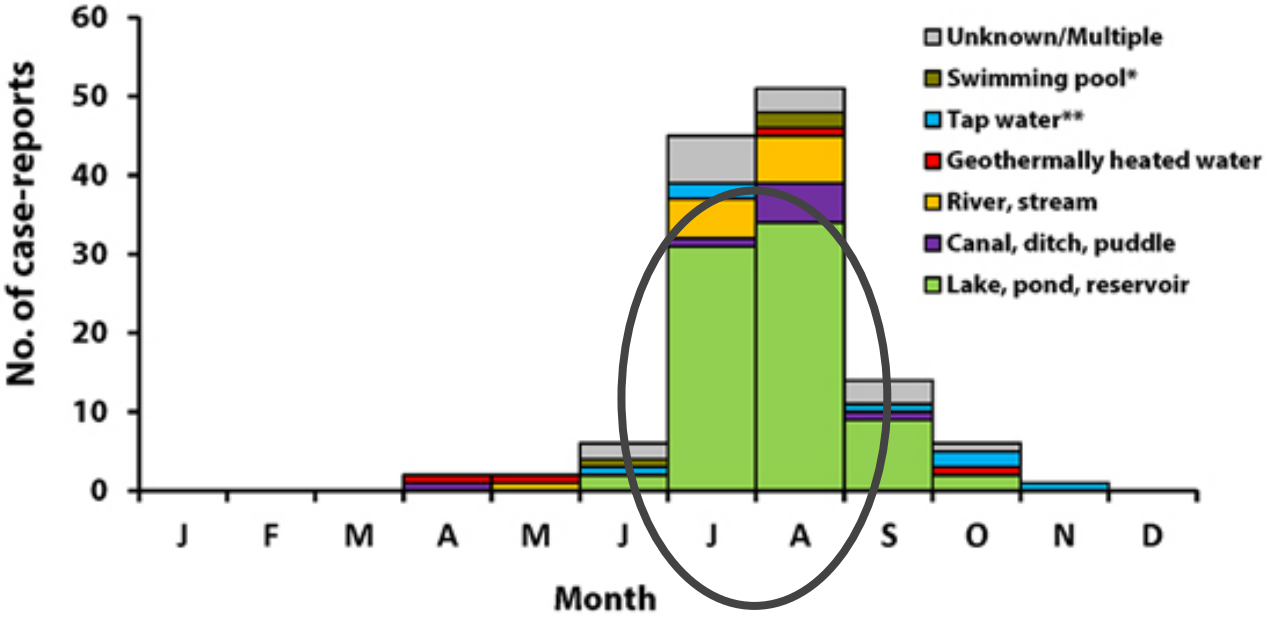
- PAM more common in warmer regions and warmer months

Over half of reports in Florida and Texas





Epidemiology: Infection by Month



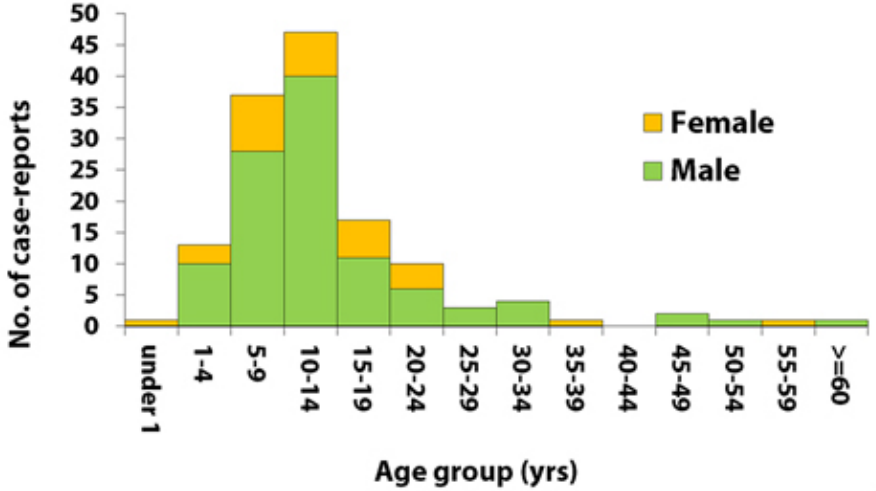
Epidemiology: Demographics

Can infect all age groups but 83% in children

Most common in first 3 decades

Male to Female ratio of PAM is 2:1

Male to Female ratio of GAE is 5:1



Conclusion

PAE is a result of infection by *N. fowleri's* invasion of the cranium through the cribiform plate, where it quickly overwhelms tissue and causes lesions in the brain. Similarly also caused by amoebas *Acanthamoeba* and *B. mandrillaris* in immunocompromised patients, is Granulamatous Amoebic encephalitis.

Both pathologies present with typical signs of CNS pathology including altered mental status and neurological dysfunction

Both diseases have similar epidemiologies, treatment, and prevention.

There are extremely rarely reported cases, most presenting in young children, and endemic to regions with warm bodies of water

Treatment includes administration of anti-leshmanias like miltefosine

References

Schuster FL, Guglielmo BJ, Visvesvara GS. In-vitro activity of miltefosine and voriconazole on clinical isolates of free-living amebas: Balamuthia mandrillaris, Acanthamoeba spp., and Naegleria fowleri.External Web Site Icon J Eukaryot Microbiol. 2006;53:121-6.

Linam WM, Ahmed M, Cope JR, Chu C, Visvesvara GS, da Silva AJ, Qvarnstrom Y, Green J. Successful treatment of an adolescent with Naegleria fowleri primary amebic meningoencephalitis.External Web Site Icon Pediatrics. 2015;135:e744.

Goswick SM, Brenner GM. Activities of azithromycin and amphotericin B against Naegleria fowleri in vitro and in a mouse model of primary amebic meningoencephalitis. *Antimicrob Agents Chemother*. 2003 Feb. 47(2):524-8.

Dorlo T, Balasegaram M, Beijnen J, Vries P. Miltefosine: A review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. Research Gate. https://www.researchgate.net/figure/230570941_fig2_figure-3-antileishmanial-mechanism-of-action-of-miltefosine-the-various-proposed. Published July 2012. Accessed July 26, 2016.

References Continued

Centers for Disease Control and Prevention

http://www.cdc.gov/parasites/acanthamoeba/amebic-encephalitis.html

Instabeat
http://www.instabeat.me/blog/2013/01/03/pros-and-cons-of-wearing-a-nose-clip-while-swimming/

Naegleria fowleri — Primary Amebic Meningoencephalitis (PAM) — Amebic Encephalitis. CDC. http://www.cdc.gov/parasites/naegleria/infection-sources.html. Published April 22, 2016. Accessed July 26, 2016.

Tolan RW. Amebic Meningoencephalitis. MedScape. http://emedicine.medscape.com/article/996227-overview#a7. Published November 17, 2015. Accessed July 26, 2016.

Mayer P, Larkin J, Hennessy J. Amebic encephalitis. *NCBI.* April 2011. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc3114370/. Accessed July 26, 2016.