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Wisconsin and Washington

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# NAEGLERIA AND ACANTHOMOEBA

## INTRODUCTION

Free living amebae from two genera, *Naegleria* and *Acanthomoeba*, are known to cause disease in humans and other mammals. A rapidly fatal disease, most often called primary amebic meningoencephalitis (PAM), usually is caused by the ameboflagellate *Naegleria fowleri*. This *Naegleria* infection occurs mostly in active young people (swimmers) without any recognized predisposing condition.

Primary amebic meningoencephalitis was first described in 1966, but human PAM has been found in retrospective studies as early as 1937 near Richmond, Virginia. The earliest known example of human PAM was found in a brain preserved in 1909 in England.

Pathogenic free-living amebae such as *Naegleria* share with other small free-living amebae a relatively simple life cycle: a)vegetative trophozoite, feeding mostly on bacteria in nature, b) a resistant cyst phase, often able to resist dessication indefinitely, and c) in *Naegleria*, a transient flagellate phase. With *Naegleria* it appears that the flagellate can enter the nose of a swimmer and rapidly revert to an invasive trophozoite.

Since first being described and to date, approximately 129 cases of PAM have been documented worldwide; 56 of these cases from the United States. In 1987, CDC recorded: 2 cases in Arizona, 1 in Louisiana, 1 in South Carolina, and 1 in Texas. Case histories and animal experiments demonstrate a direct route of cranial invasion through the olfactory mucosa and cribriform plate along the olfactory nerve.

## CLINICAL ASPECTS OF FREE-LIVING AMEBIC INFECTIONS[1]

Primary infection by the ameba, *N. fowleri*, in humans usually involves the central nervous system. The disease process is a primary amebic meningoencephalitis. PAM usually occurs in children and young adults who previously have been in good health. Victims usually have had a recent history of swimming in heated swimming pools or man-made lakes, or some contact with mud or brackish, muddy water. However, cases have been reported with no apparent water contact.

Sub-clinical infections due to free-living amebae are possible in healthy individuals, with the protozoa living in the nose and throat. Recent reports[2] in the dental literature report isolation of *Naegleria* in the dentition and month. It is also possible that antibodies and cell-mediated immunity protect some individuals against acute infections in ordinary circumstances.

## PORTAL OF ENTRY AND PATHOGENESIS

The pathogenic amebas probably enter the nasal cavity by inhalation or aspiration of water containing the trophozoites or cysts. Inhalation or aspiration of aerosols containing cysts is another possible source of infection. Respiratory symptoms may be the result of sub-clinical infection or hypersensitivity. The olfactory neuro-epithelium is the principal route of invasion, and usual anatomical site of the primary lesion, of PAM due to *N. fowleri*. The histopathological characteristics include: 1) destruction of the olfactory mucosa and olfactory bulbs and 2) hemorrhagic necrosis of both grey and white matter, with an inflammatory infiltrate consisting of abundant polymorphonuclear leukocytes, eosinophils, and few macrophages. Only trophozoites are found in the lesions.

  

**INCUBATION PERIOD**

The period of time between the initial contact with amebae and clinical symptoms is considered three to 15 days, with the usual time about seven days.

**SIGNS AND SYMPTOMS**

PAM is a disease characterized by an abrupt and fulminant course leading almost invariably to death. The symptoms are associated primarily with severe meningeal irritation and consist of severe headache, stiff neck, fever (39° C-40° C; 102.2° F-104° F), and vomiting. Pharyngitis or symptoms of nasal obstruction and discharge are less frequent. An occasional complaint the first day or so is a distortion of taste or smell. Headache, vomiting, and fever persist, but within two to four days after onset, drowsiness, confusion, and neck stiffness develop. Convulsions may occur but have not been pronounced in most cases. Progressive deterioration follows, leading to deep coma with minimal if any neurological signs. The vast majority of cases have ended fatally about one week after the appearance of the first symptoms.

The diagnosis is established by finding trophozoites in the spinal fluid. The peripheral white cell count is usually elevated with a shift to the left. The spinal fluid is usually purulent with a preponderance of neutrophils, resembling an acute bacterial infection. The protein content almost always is markedly elevated in the range of 100 to 1,000 mg/mL. The glucose content can be normal to mildly reduced. A wet mount of the spinal fluid may demonstrate motile amebae.

**DIFFERENTIAL DIAGNOSIS**

No distinct differences exist which will allow differentiation of PAM from acute pyogenic or bacterial meningoencephalitis on clinical grounds. The history of previous good health and recent swimming in fresh water should raise the index of suspicion, especially during the hot summer months. Computed tomographic scans show obliteration of the cisterns surrounding the midbrain and the subarachnoid space over the hemispheric convexities. Marked enhancement occurs with administration of intravenous contrast medium.

**TREATMENT**

Many different therapeutic regimens have been tried for the treatment of acute PAM but, to date, most have been unsuccessful. One case was treated successfully with a regimen of AMPHOTERICIN - B intravenously and intrathecally (25-50 mg/kg/day IV, 0.1 mg I/T every other day). The addition of rifampin, miconazole, and tetracycline have been used, and there is some evidence of synergism. The possibility of cure depends on early, accurate diagnosis with very aggressive therapy. If there is a clinical pearl to pass on, it is to have a high degree of suspicion and do a wet-field examination of the spinal fluid to establish the diagnosis of PAM.

**Editorial Note:** Human *Naegleria* infections generally occur during warm weather and following contact with warm or previously warmed water. In most infections worldwide, the water contacted had been chlorinated. In the United States, most cases occurred following summertime activities in fresh water lakes and streams.

The use of chlorine in swimming pools may provide some protection, although the amount of chlorine necessary to kill *Naegleria* cysts or trophozoites is the subject of debate in the literature. Certainly, it will take less chlorine to kill the unprotected trophozoite stage, whereas, the encysted amoeba, being protected by the reasonably thick and protective cyst wall, will be able to withstand higher concentrations.[3] Some reports indicate that the growth of *Naegleria* in swimming pools can be prevented by 0.5 ppm to 1.0 ppm of chlorine. *Naegleria fowleri* cysts have been shown to be killed within one hour of contact by 0.5 ppm chlorine, which can be readily achieved in water supplies or pools. Other reports in the literature state that chlorine as high as 10.0 ppm failed to clear *Naegleria* from swimming pools.[4] As regards control measures, one source indicates that maintaining a salinity of 0.7% weight per volume in a swimming pool will prevent the colonization of the pool by *Naegleria.*[4]

A closely related amoeba, *Acanthamoeba* spp, can also cause PAM. PAM caused by *Acanthamoeba* spp, while potentially as fulminating, tends to follow a more chronic course. Recently, the literature has described many cases of *Acanthamoeba* keratitis, an eye infection caused by this ubiquitous amoeba. These cases are most often associated with the use of extended-wear contact lenses and cleaning solutions which become contaminated with the amoeba.

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## CHILDHOOD CHLOROQUINE POISONINGS -- WISCONSIN AND WASHINGTON*

Each year the approximately 1 million Americans who travel to malarious areas may be advised to take chloroquine weekly for prophylaxis. In addition, chloroquine is prescribed as therapy for certain connective tissue disorders. Consequently, there are many opportunities for children to be poisoned through chloroquine ingestion. To alert medical practitioners and the public to this danger, the following cases of chloroquine poisoning recently reported to CDC are presented.

**Case 1.** On August 6, 1987, a previously healthy 20-month-old girl was found unresponsive next to an opened empty bottle of chloroquine phosphate. The chloroquine remained from a supply dispensed to the child's grandfather for malaria prophylaxis. The amount of chloroquine base the child swallowed was estimated at 800 mg.

Shortly after the emergency medical technicians arrived, the child suffered cardiac arrest. Normal sinus rhythm was restored en route to the emergency room, but persistent hypotension necessitated intravenous dopamine. The child began to have generalized seizures 1 hour after ingestion; these were controlled with intravenous diazepam, phenytoin, and phenobarbital. Charcoal hemoperfusion performed 7 hours after ingestion did not improve her condition. Serum chloroquine concentrations before and after the procedure were 0.8 and 0.3 $\mu$g/mL, respectively (2.5 and 0.94 $\mu$ mol/L). Over the next week her neurologic condition gradually improved, and mechanical ventilation was discontinued after the eighth day of hospitalization. Subsequent cranial computerized tomography scans and electroencephalography revealed atrophy and decreased voltage consistent with postanoxic encephalopathy. Rehabilitative efforts continue; currently, she is able to make some purposeful movements but still requires feeding by gastrostomy.

**Case 2.** On January 20, 1988, a 17-month-old boy ingested 2.4g of chloroquine base. His parents had recently returned from a tour of duty in Cameroon during which they had been taking chloroquine for malaria prophylaxis; the chloroquine had been dispensed in Cameroon in an envelope. The child was immediately taken to an emergency room, but 30 minutes after ingestion, ventricular tachycardia, hypotension, apnea, and seizures developed. After two hours of resuscitation, his condition was stabilized on intravenous epinephrine and diazepam.

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*Reprinted from: CDC. MMWR 1988; 37(28): 437-9.

Serum chloroquine concentration 11 hours after ingestion was 1.0 µg/mL (3.1 µmol/L). His condition improved slightly during the next three weeks, and he was gradually removed from ventilator support after one month. However, he remains unconscious with no purposeful movement.

**MMWR Editorial Note:** When used for prophylaxis and treatment of malaria, chloroquine has proven to be safe in the recommended dosage range (5-25 mg/kg body weight). However, a relatively small increase in the therapeutic dose is toxic; children who have ingested two to three times the recommended treatment dose have been fatally poisoned. Chloroquine is rapidly absorbed from the gastrointestinal tract. Consequently, as the second case illustrates, the interval between ingestion and cardiorespiratory collapse is frequently less than 2 hours.

A recent review of 91 cases of chloroquine poisoning in which blood concentrations were determined revealed that no patient survived in whom blood concentrations were greater than 25 µ mol/L. Since the drug is extensively tissue-bound, concentrations in the liver and kidney are generally many times higher than those in the blood. The extensive tissue binding makes dialysis largely ineffective in removing the drug.

The toxic effects of chloroquine are related to its depressant effect on the myocardium, resulting in decreased cardiac output and hypotension. Like quinidine, the drug reduces the excitability and conductivity of cardiac muscle, and at toxic concentrations profound bradycardia with ventricular escape rhythms may occur.

Animal toxicology data and case studies of suicide attempts with chloroquine suggest that sympathomimetic agents may decrease the hemodynamic and electrophysiologic cardiotoxic effects of chloroquine. Diazepam has been found to decrease the mortality rate in experimental chloroquine poisoning in rats. A recent study examined the clinical utility of immediately administering intravenous diazepam and epinephrine in chloroquine poisoning. Ten of eleven patients who ingested more than 5 g of chloroquine and were treated with diazepam and epinephrine survived, as compared with 1 of 51 retrospective controls who ingested comparable dosages.

Health-care providers should be aware of the potential interventions to prevent chloroquine poisoning. Chloroquine prescriptions should be written for the precise amount needed for prophylaxis for each trip to avoid accumulation of extra tablets. Any drug remaining after prophylaxis is complete should be safely discarded. Chloroquine should be dispensed in child-proof containers, particularly when young children are in the home.

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