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Case Report

Primary Amoebic Meningoencephalitis in Kerala – An Emerging Public Health Concern

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A B S T R A C T

Primary Amoebic Meningoencephalitis (PAM) is an acute and often fatal infection of the brain caused by the free-living amoeboflagellate *Naegleria fowleri*. These amoebae are ubiquitous and are found naturally in freshwater environments, such as pools, ponds, canals, lakes, and rivers. They are commonly called the 'brain-eating amoeba' because they can cause a brain infection when water containing the amoeba moves into the nose. PAM is often found in immuno-competent children and young adults, especially after exposure to amoeba-contaminated water. Its increasing incidence is reported worldwide. PAM is set apart by a mortality rate of 98% and the high mortality has been imputed to a rapid onset of the illness, delayed diagnosis, and lack of effective treatment protocol. In Kerala, the first confirmed PAM case was reported in the Alappuzha district in March 2016, and since then seven more cases were reported from the state, and all of them succumbed to the infection. The deadly clinical condition is often misdiagnosed and is grossly under-reported. This highly necessitates that ample awareness and education should be given to the healthcare providers and the public about the aetiology of the illness with special emphasis on the mode of transmission and clinical presentations. This article discusses the various *N. fowleri* cases reported in Kerala along with their geo-demographic details and epidemiological and pathological information. It emphasises the need for public health awareness and intervention activities to prevent the occurrence and spread of the disease in Kerala.

Keywords: Primary Amoebic Meningoencephalitis, Pathological Information, *Naegleria fowleri*

Introduction

Primary amoebic meningoencephalitis (PAM) is a severe and often fatal central nervous system (CNS) infection caused by *Naegleria fowleri*, a free-living flagellate amoeba found in the environment mainly in soil and freshwater.[1] This amphizoic organism was first described by Fowler and Carter from Australia in 1965.[2] This amoeba is thermophilic and thrives in freshwater at high temperatures. *N. fowleri* infects people when the water containing amoeba enters the body through the nose. This normally occurs when people go swimming or diving in ponds, canals, and rivers. The amoeba enters the nasal cavity, attaches to the nasal mucosa, pierces into it, and crosses the cribriform plate into the olfactory bulb. The repercussions of brain penetration lead to brain inflammation, herniation of the brain artery, and ultimately death.[3] The life cycle of this pathogenic amoeba has three stages, namely cyst, trophozoite, and flagellate. The trophozoite is the only form of *N. fowleri* that can reproduce, feed, and cause infection in other organisms. The infection is acute and usually fatal and its diagnosis is often made at autopsy.

A total of 39 countries have reported cases of *N. fowleri* infections. However, the most affected countries include the United States of America (USA), Pakistan, Mexico, Australia, the Czech Republic, and India. The year-round warm climates and access to contaminated water sources associated with the attitude of the people towards water exposure activities have been ascribed to play a significant role in the increase of incidences of PAM cases in the aforementioned countries. From 1962 to 2018, 381 cases were reported worldwide, of which 26 cases were from India.[4] Three cases were reported from Kerala earlier.[5,6] The recent findings on *N. fowleri* infections reported from Kerala provide the latest updates about the illness and enable clinicians and public health specialists to be more informed and require planning appropriate intervention activities.

Cases Reported from Kerala - Observations and Discussion

A fatal case of PAM was diagnosed in a 16-year-old male child residing in Alappuzha district, Kerala in March 2016. The child presented with a history of frontal headache, vomiting, high fever, neck rigidity, excessive drowsiness with altered sensorium, and irrelevant talk. This was the first confirmed PAM case reported in Kerala. A total of eight confirmed PAM cases have been reported from Kerala so far (2 cases from Alappuzha, 2 cases from Thrissur, 3 cases from Malappuram, and 1 case from Kozhikode district) (Figure 1).

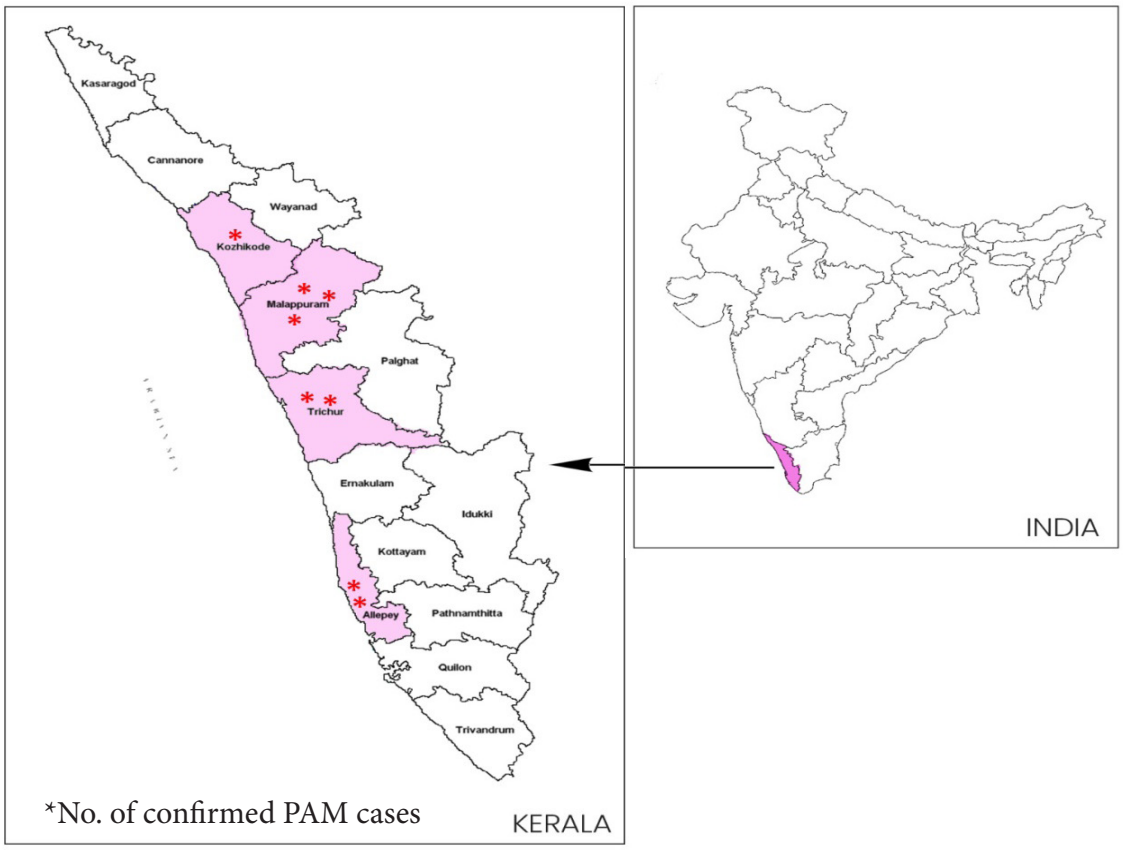

Figure 1.Districtwise Confirmed Primary Amoebic Meningoencephalitis Cases Reported in Kerala

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Of the eight confirmed PAM cases reported in Kerala, seven were male (87.5%) and one was female (12.5%). Patients' ages were heterogeneous ranging from 10 to 62 years old, with a median age of 26 years. While reviewing the geo-demographic and epidemiological characteristics of PAM cases reported worldwide, the observations of most of the investigators are on par with the aforementioned result.[4,7] Increased numbers of *N. fowleri* infections in males might be associated with their behaviour, especially the habit of swimming in pools, ponds, canals etc. The difference in the immune response of the individuals leading to an increased risk in males is a matter of further study. A sedulous examination of the history of disease onset can increase the possibility of achieving the probable diagnosis. In the present study, it has been observed that of the total 8 cases, 5 (62.5%) had clear exposure in the form of swimming and diving in contaminated water bodies and 2 (25%) had the habit of ritual nasal rinsing with untreated tap water and in the remaining 1 case (12.5%), the source or mode of exposure is not known. In recent studies, it has been noted that the most significant factor associated with the risk of disease transmission was water contact activities such as swimming, diving, bathing, water sports,[4,8–11] and ritual nasal rinsing.[12–14]

On the basis of the onset of *N. fowleri* infections reported in India and elsewhere, it has been postulated that global warming will further change the environmental distribution of *N. fowleri* and cause greater proliferation of the organism potentially leading to more infections.[15,16] The earlier studies showed that a majority of case exposures were specifically reported during warm, hot or summer seasons. This is in accordance with the thermophilic nature of *N. fowleri*.[1]

The duration of the summer season in Kerala is from February to May, with temperatures rising to 35° and beyond. The main rainy season in Kerala is extended from South West Monsoon (June to August) to North East Monsoon (October to November). Of the known onset period of *N. fowleri* infections reported in Kerala, three cases were reported in the month of June and one case each was reported in March, May, August, and November. Thus in Kerala, a majority of the cases (71.4%) were reported either at the beginning of the rainy season or in its fading period. Only two cases (28.6%) were reported during the summer season. This is due to the prevailing high water temperature during the fading phase of summer and the beginning spell of monsoon. However, the phase of *N. fowleri* infections in Kerala in relation to climatic conditions is yet to be studied in detail. A detailed study by analysing the precise geographical distributions of PAM cases might enable understanding the climate-related variability in risk.[4] Earlier reports indicated that the geographic pattern of this climate-sensitive, thermophilic amoeba appears to be changing. Thus, systematic monitoring is required to understand and predict the potential changes in *N. fowleri* ecology in different water habitats where people go for swimming, diving, and other recreational activities.[17] This task requires elaborate procedures involving field-level implementation.

PAM develops after several days of exposure to contaminated water sources. So the assessment of the period between exposure to water sources and the manifestation of signs and symptoms is often a challenging issue. The study related to the epidemiology of *N. fowleri* infections indicated that the clinical presentations usually appear 5–7 days after the initial exposure but may also develop after only 24 hours.[18] It has been noted in the present study that the disease phase lasts for an average of 6 days and death occurs 4–11 days after onset (Table 1). While studying the epidemiology of PAM cases reported in the USA, Yoder et al. noted that as the disease progresses, neurological symptoms such as confusion, seizures and coma follow and the patients usually succumb within 5–10 days.[19] The same is true in the PAM cases reported from Kerala as well.

The analysis of the epidemiological details of the present study indicated that all the infected individuals showed frontal headache and fever. The other clinical presentations included vomiting (87.5%), neck rigidity (75.0%), drowsiness (50.0%), altered sensorium (50.0%), irrelevant talk (37.5%), photophobia (37.5%), convulsions (12.5%), urinary incontinence (12.5%) and cough (12.5%) (Table 1). Earlier reports also indicated fever, headache, and vomiting as the most common symptoms in N. fowleri-infected cases.[7]

The analysis of the vital signs of N. fowleri-infected cases reported in Kerala indicated that the median pulse rate was 95 bpm (2–118 bpm) and the median blood pressure was 115/71 mmHg (100/60–140/90 mmHg). White blood cell counts were elevated (median: 18577 cells/µL, range: 15,000–22,700 cells/µL), of which neutrophils were 86%, lymphocytes were 7%, and eosinophils were 7%, and platelet count showed the following values: median: 3.29 lakh, and range: 2.29–4.28 lakhs (Table 1).

During the inceptive stages of infection, computed tomography (CT) scans and magnetic resonance imaging (MRI) are useful in diagnosing brain infections in the form of cerebral oedema and cortical sulcal effacement. The microscopic examination of cerebrospinal fluid (CSF) stained with Giemsa is useful in identifying *Naegleria* trophozoites.[20] Another technique for identifying *N. fowleri* trophozoites is culturing CSF samples in nutritive agars to obtain axenic cultures of amoebae. CSF sample results may help to obviate the viral aetiology of CNS involvement. Diagnosis could also be made by recovering motile trophozoites from the nasal cavity by washing it with saline solution.[21] In the present study, CSF findings indicated that red blood cells were elevated (median: 1364 cells/µL, range: 192–2700

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cells/µL). White blood counts were also elevated (median: 5289 cells/µL; range: 300–14,500 cells/µL); these were predominantly neutrophils (median: 72%, range: 52–92%) followed by lymphocytes (median: 23%, range: 8–48%). The CSF of most patients was characterised by elevated protein (median: 635 mg/dL, range: 248–1100 mg/dL) and low glucose (median: 20 mg/dL, range: 1–62 mg/dL) (Table 1). Earlier reports also showed a similar pattern while dealing with the pathogenesis of *N. fowleri* infection.[4,7] It is to be noted that low CSF glucose levels and associated high levels of CSF proteins rule out viral causes. The CSF findings, most often, may be inadequate for legitimate clinicians to distinguish PAM cases from other infectious causes of meningitis. However, the presence of predominantly neutrophilic elevated white blood cell count, increased protein, and low glucose should activate a surmise for PAM in addition to bacterial meningitis.

In a majority of PAM cases (87.5%) described in the present study, wet mount preparation of CSF stained with Giesma showed amoebic trophozoites resembling N. fowleri. An attempt was also made to collect and examine the water samples from the exposure site. In the present study, samples were collected from five water bodies with clearly known sources of infection. However, only two samples (40%) showed positive results for growth of amoeba resembling *N. fowleri* (Table 1). In order to isolate the pathogenic amoeba from the source of infection, water samples should be taken from the source immediately after the case report; otherwise, the changes in the environmental biotic and abiotic factors may adversely affect the distribution and abundance of N. fowleri.[22] Delayed sample collection may result in either the absence of amoeba or an inconclusive outcome in the laboratory examination. Hence timely collection and examination of water samples from the exposed site is of paramount importance in confirming the presence or absence of N. fowleri. A precise diagnosis is critical because assertive treatment can be commenced rapidly to ensure survival.

Among the eight cases reported, initially, the treatment was given for acute pyogenic meningoencephalitis in three of the cases, and in one case, the treatment was commenced for acute bacterial meningitis. Later all the cases were confirmed as PAM. The most common medications administered were amphotericin B (75%), fluconazole (37.5%), rifampicin (25%), azithromycin (50%) and miltefosine (12.5%) (Table 1). The challenges in diagnosing PAM cases in a clinical setting, especially in the early phase of onset, might have contributed to the underestimation or underreporting of the infection. The initial vague presentation and subsequent presentation that mimics bacterial meningitis may prevent clinicians from making a correct diagnosis. Hence the number of undiagnosed cases may be even higher in countries where they do not have a surveillance network system for PAM or proper diagnostic testing facilities.

A high degree of perception regarding the mode of transmission is required to diagnose PAM. The first PAM case from Kerala was reported in 2016. The father of the 16-year-old patient repeatedly told the paediatrician who attended the case that the boy developed this disease only after taking a bath in the polluted canal in front of their house. Therefore, a CSF sample was examined and diagnosed as *N. fowleri* infection. This is a classic example of the keen observation of the parent and its significance in triggering the perception of the doctor in identifying one of the most rare and fatal diseases in the world.

The prevalence of *Naegleria fowleri* was already reported in water samples from India.[23,24] In our investigations of the first case reported in 2016 and the last case reported in 2023, the water samples collected from the canals where the patients used to take a bath showed growth of amoeba resembling N. fowleri, which indicated that *N. fowleri* is widespread in our water bodies, which is a cause of concern.

In order to avoid high fatality associated with *N. fowleri* infection, comprehensive public health measures should be taken. The public needs to be educated about the illness and the mode of transmission of the disease through continuous health awareness programmes. Health education materials prepared in local languages should be widely circulated to encourage the public to seek immediate treatment if they start developing symptoms after water-based recreational activities.

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Table 1.Geo-demographic Details, Epidemiological Observations, Pathological Information and History of Reported *Naegleria fowleri* Cases in Kerala

Case No.	Geo-demographic Details			Epidemiological Observations				Pathological Information		Diagnosis and Treatment		
	Month, Year	Age (Years), Gender	Locality, District	Infection Period (Days)	Clinical Presentations	Source/ Exposure	Vital Signs	CSF Profile	Diagnostic Methods	Diagnosis/ Interpretations	Treatment	Post-treatment History
1	Mar, 2016	16, M	Alappuzha Municipality, Alappuzha District	6	Frontal headache, vomiting, high fever, neck rigidity, excessive drowsiness, altered sensorium, and irrelevant talk	Canal swimming and diving	PR: 88 bpm, BP: 100/60 mmHg, AEBE clear, Hernings sign: –ve, Hb: 13.4 g/dL, WBC: 16800 cells/mm^3 (PMC: 88.6%, L: 4.1%, E: 7.3 %), ESR: 20	TC: 850 cells/mm^3 (N: 62.0%, L: 38.0%), SL: < 0.165 mmol/L, P: 5.05 g/L	DE, CSF Giemsa staining, NNE	Wet mount preparation of CSF and Giemsa stain of CSF showed amoebae with features morphologically suggestive of *N. fowleri.* The culture of water samples from the canal in non-nutrient agar plates seeded with a thin layer of E. coli showed the growth of amoebae resembling *N. fowleri.*	Ampho-tericin B (intravenous and intrathecal), fluconazole, azithromycin and rifampicin	Died on the 6th day of illness

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2	May, 2019	10, F	Angadi-puram Munici-pality, Malap-puram District	4	Frontal headache, vomiting, high fever, neck rigidity, drowsiness, altered sensorium, disorientation, and photophobia	No history of swimming or diving in ponds, rivers or streams	PR: 86 bpm, BP: 126/66 mmHg, Temp: 98.6°, RR: 28/min	WBC: 444 cells/mm^3, (N: 52.0%, L: 48.0%), RBC: 192 cells/mm^3, SL: 98 mg/dL, P: 300 mg/dL	DE	Wet mount preparation of CSF showed amoebic trophozoites resembling N. fowleri.	Treated for acute bacterial meningitis	Died on the 4th day of illness
3	Jun, 2020	13, M	Kondotty Muni-cipality, Malap-puram District	7	Headache, fever, vomiting, neck rigidity, disorientation, and irrelevant talk	Pond swimming and diving	PR: 118 bpm, BP: 110/80 mmHg, AEBE clear, Hb: 12.7 g/dL, WBC: 22700 cells/mm^3 (N: 86%, L: 7%, E: 7%), RBC: 5.13 million/mm^3, platelets: 4.28 lakhs	SL: 1 mg/dL, P: 479.4 mg/dL, WBC: 14500/ mm^3 (PMC: 90%, L: 10%), RBC: 1200 cells/ mm^3	CT Brain, EEG	CT brain was suggestive of cerebral oedema. EEG records showed severe diffuse cerebral dysfunction suggestive of N. fowleri infection.	Treated for pyogenic meningitis. antibiotics (inj. vancomycin and inj. ceftriaxone)	Died on the 7th day of illness

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4	Jun, 2020	12, M	Kozhi-kode Corpo-ration, Kozhi-kode istrict	5	Headache, fever, drowsiness, dizziness, vomiting, urinary incontinence, irrelevant talk, neck rigidity, altered sensorium, convulsions, positive meningeal signs, and encephalopathy	Swimming and diving in an artificial pool made on the home terrace	Positive meningeal signs, irritability, and ence-phalopathy	WBC: 1800 cells/mm^3 (N: 80%, L: 20%), SL: 5.5 mmol/L, P: 2.6 g/L	DE	Wet mount preparation of CSF showed amoeboid trophozoites, which confirmed the diagnosis of PAM. CT brain showed diffuse cerebral oedema with early uncal herniation.	Amphotericin B, azithromycin, rifampicin, ceftriaxone, acyclovir	Died on the 5th day of illness
5	2021	62, M	Thrissur District	11	Headache, fever, sudden onset of clonic seizures, recurrent episodes of vomiting, and photophobia	Pond swimming	PR: 110 bpm, BP: 140/90 mmHg, WBC: 15000 cells/mm3 with PMC: 80%, ESR: 40 mm/h, oxygen saturation: 98%, random blood sugar: 324 mg/dL, serum sodium: 126 mEq/L	SL: 62 mg/dL, P: 248 mg/dL, leukocytosis (10000 cells/mm3) with 90% polymorphs	DE	Wet mount preparation of CSF showed numerous motile amoebic trophozoites suggestive of N. fowleri.	Amphotericin B, azithromycin, rifampicin, fluconazole and miltefosine	Died on the 11th day of illness

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6	Nov, 2021	42, M	Cherukavu Panchayat, Mala-ppuram District	4	Frontal headache, high fever, drowsiness, vomiting, neck rigidity, altered sensorium, and seizures	Practised nasal rinsing before prayers 5 times every day	NA	SL: 12 mg/dL, P: 713 mg/dL, WBC: 9400 cells/mm^3 (N: 92.0%, L: 8.0%), RBC: 2700 cells/mm^3	DE	Wet mount preparation of CSF showed amoebic trophozoites and was confirmed post-death as N. fowleri.	Treated for acute pyogenic meningoen-cephalitis with parenteral ntibiotics, antiepileptics, cerebral decongestants and supportive measures	Died on the 4th day of illness
7	Aug, 2022	36, M	Desa-mangalam Panchayat, Thrissur District	4	Severe headache, high fever, altered sensorium, neck rigidity, seizures, and drowsiness	Practised nasal rinsing before prayers 5 times every day	PR: 72 bpm, BP: 100/60 mmHg	SL: 5 mg/dL, P: 1100 mg/dL, WBC: 300 cells/mm^3 (PMC: 61.0%, L:39.0%)	DE, CT brain	Wet mount preparation of CSF showed motile trophozoites resembling N. fowleri. CT brain showed cerebral oedema.	Treated for acute meningoen cephalitis with parenteral antibiotics (ceftriaxone), acyclovir and symptomatic management)	Died on the 4th day of illness

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8	Jun, 2023	15, M	Panavally Panchayat, Alappuzha District	8	Fever, headache, cough, vomiting, photophobia, and altered sensorium	Canal swimming and diving	Hb: 12.1 g/dL, WBC: 18030 cells/mm^3 (N: 86.2%, L: 4.4%, E: 0.1%, B: 0.3%, M: 9.0%), platelets: 2.29 lakhs	NA	DE, NNE	Wet mount preparation of CSF showed motile trophozoites and Giemsa-stained slides showed amoebic presence suggestive of N. fowleri. The culture of water samples from the canal in non-nutrient agar plates seeded with a thin layer of E. coli showed the growth of amoebae resembling N. fowleri.	Managed with inj. azithromycin, fluconazole, Dexona, ceftriaxone, tab rifampicin and IV fluids	Died on the 8th day of illness

AEBE: Air Entry Bilaterally Equal, BP: Blood Pressure, CSF: Cerebrospinal fluid, CT: Computed Tomography, DE: Direct CSF Examination, EEG: Electroencephalogram, Hb: Haemoglobin, L: Lymphocytes, B: Basophils, M: Monocytes, N: Neutrophils, NNE: Non-nutrient Agar with E. coli culture, E: Eosinophils, ESR: Erythrocyte Sedimentation Rate, P: Protein, PMC: Polymorphocytes, PR: Pulse Rate, RBC: Red Blood Cells, SL: Sugar Level, TC: Total Count, WBC: White Blood Cells, M: Male, F: Female

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Conclusion

It should be noted that despite the proven prevalence of these free-living amoebae in freshwater bodies, only very few cases are reported from India. This fatal clinical condition is often misdiagnosed as bacterial meningitis. Its cases are increasing throughout the world and it is becoming a cause of concern. To date, eight cases have been reported from Kerala and all succumbed to the infection. Rapid progression of the disease process and limited awareness among the medical fraternity make this disease a diagnostic challenge and it is likely that many cases might have gone undetected. Therefore, practical measures for the prevention and control of PAM such as education of the public, awareness within the medical community and regular surveys of water sources for *N. fowleri* are urgently needed.

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