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Review Article

A scoping review on epidemiology and pathogenesis of death due to primary amoebic meningoencephalitis

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ABSTRACT

Primary amoebic meningoencephalitis (PAM) also known as Naegleriasis is a lethal central nervous system disorder caused by the amoeba *Naegleria fowleri* and spreads through contaminated water bodies. Nasal cavity is the route of entry for the infective form trophozoite. It is a fatal disease as the earlier diagnosis is missed due to its resemblance with Bacterial meningitis. This is a trial to record the pathogenesis of death due to PAM from available literatures. 22 research articles reported with death due to PAM had been reviewed and results documented. Out of 45 patients, most of them had contact with contaminated water bodies and all the investigations available showed cerebral oedema. Most of the cases had contact with contaminated water bodies which shows the need of decontamination of water bodies. Late diagnosis of most of the cases due to resemblance of symptoms with bacterial meningitis is also a cause for lethality.

Keywords: Amoeba, Brain oedema, Decontamination, *Naegleria fowleri*, Naegleriasis, Primary amoebic meningoencephalitis

INTRODUCTION

Primary amoebic meningoencephalitis (PAM) caused by the amoeba *Naegleria fowleri*, (*N. fowleri)* also known as 'brain-eating amoeba'. It is a rare, lethal central nervous system disorder leading to oedema of brain. *N. fowleri* can live up to temperature of about 45.8°C while the other amoeba cannot. Hence, a temperature of 45°C is used to isolate *N. fowleri* species while it suppresses the growth of another amoeba. As the amoeba is heat- resistant it is most commonly seen in warm water sources and it cannot survive in salt water such as sea water.

Most of the infection occurs during summer. The infection spreads through contaminated water bodies and death occurs within 1-2 weeks.[1] Nose of humans are the only route of infection.[1-3] The infection occurs when water containing trophozoite is drawn through the nose. The pathogenesis depends on the site of the body where the trophozoites travel. In brain it leads to necrotising encephalitis leading to damage of brain parenchyma. The symptoms resemble those that of bacterial meningitis.

The amoeba is found in three morphological forms namely trophozoites, flagellates and cysts. Trophozoites are the infective form. The diagnosis is very rarely made before the death. The preventive measures include avoiding jumping or diving in to the stagnant water, using nose plugs while diving or swimming, keeping the head high during swimming and proper decontamination of water sources.[1,4]

There are so many case reports published with cases of primary amoebic meningoencephalitis. Only few studies are conducted regarding the epidemiology and pathogenesis of death in PAM. A trial is made to record the epidemiology and pathogenesis of death due to PAM from 45 cases published in 22 articles dated 1978 to 2024.

A literature search was conducted using the words "death in primary amoebic meningoencephalitis", "death due to primary amoebic meningoencephalitis", "primary amoebic meningoencephalitis fatality," "primary amoebic meningoencephalitis cases", "death in naegleriasis", "death due to naegleriasis", "fatality in *N.fowleri* infection", "Naegleriasis" from various databases of PubMed, Jama network, Springer nature and the Lancet. Google search engine was used to collect all relevant research articles and reports published till 2024. Twenty-two research articles were selected which includes the death cases due to PAM. Preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) checklist is used for the review of these selected articles.

Table 1: The objectives of selected articles.

S. no.	Objectives
1	The purpose of this case report is to heighten clinical awareness of PAM, share diagnostic and therapeutic insights, expand upon existing treatment approaches, and ultimately contribute to improving the survival rates of PAM patients.[5]
2	A case of PAM with diabetes insipidus is explained in this case report, where DI is a very rare complication reported in PAM.[6]
3	The goal of this case series is to advance knowledge about communicable diseases in emergency medicine and foster cooperation between the front line of clinical medicine and public health agencies.[7]
4	A death case of 56-year-old man with PAM is explained in this case report.[8]
5	Authors recommend including PAM in the differential diagnosis when CSF studies suggest bacterial meningitis but gram stain is negative. Genotyping can advance our understanding of *N. fowleri* molecular epidemiology and support future investigations.[9]
6	Need of thorough history and investigations for proper diagnosis of PAM is highlighted.[10]
7	The management strategy of PAM should be reviewed further as it is doubtful whether an era of amphotericin B-resistant Naegleria fowleri been emerged.[11]
8	The article emphasises the need for public health awareness and intervention activities to prevent the occurrence and spread of the disease in Kerala.[12]
9	Apart from focussing on different aspects of single case of PAM, this article describes 16 cases of PAM reported in China for early identification and management of the disease.[13]
10	This article emphasizes the importance of Next Generation Sequencing (NGS) in diagnosis of PAM.[14]
11	This review provides an overview of the available data and studies of free-living amoebic encephalitis in China and identify some potential difference.[15]
12	Emphasising the role metagenomic NGS in diagnosis as well as continuous renal replacement therapy in prolonging the life time of patients with multi organ failure.[16]
13	By reporting the epidemiological and environmental investigations of the case of PAM authors intend to form a framework for future epidemiological and environmental investigations.[17]
14	The authors intend to show that Naegleria spreads outside central nervous system through damaged blood brain barrier.[18]
15	To increase public awareness of the disease and maintaining high index of suspicion by healthcare professionals may help early diagnosis and timely initiation of multi-drug therapy.[19]
16	To provide awareness of PAM for early detection and management.[20]
17	To stress on the fact that possibility of PAM should always be considered in all cases of acute purulent meningoencephalitis in which no bacteria or fungus are found.[21]
18	A 3-year-old child's infection with Naegleria without any exposure is explained.[22]
19	A case of 62-year-old man died of PAM is explained.[23]
20	This case highlights the importance of epidemiological exposure and considering PAM on the differential diagnosis.[24]
21	These are the first reported PAM cases in the United States associated with the presence of *N. fowleri* in household plumbing served by treated municipal water supplies and the first reports of PAM potentially associated with the use of a nasal irrigation device.[25]
22	The isolation of *N. fowleri* in the patient calls for increased awareness among clinical and laboratory staff on suspected PAM cases to promptly diagnose and effectively manage the disease.[26]

Number of patients

Data of 45 patients died due to PAM were analysed and summarized below.

Age

The age group of all the 45 cases were documented (Table 2).

Gender

The majority of cases belongs to male group. Of the 45 cases, 42 were males and 3 were females.

History of exposure

Out of 45 cases analysed, 4 cases had no history of exposure and in 10 cases history of exposure was not known (Table 3).

Duration from exposure to production of symptoms

The duration from exposure to production of symptoms in 17 patients were documented and it ranges from 3 days to 1-2 months. Out of 17, 5 had a duration of 5 days, 3 with duration of 6 days and others with duration of weeks and months.

Clinical symptoms

The symptoms produced by 41patients were documented as follows (Table 4).

Clinical examination findings

The examination findings of 24 documented cases were as follows (Figure 1).

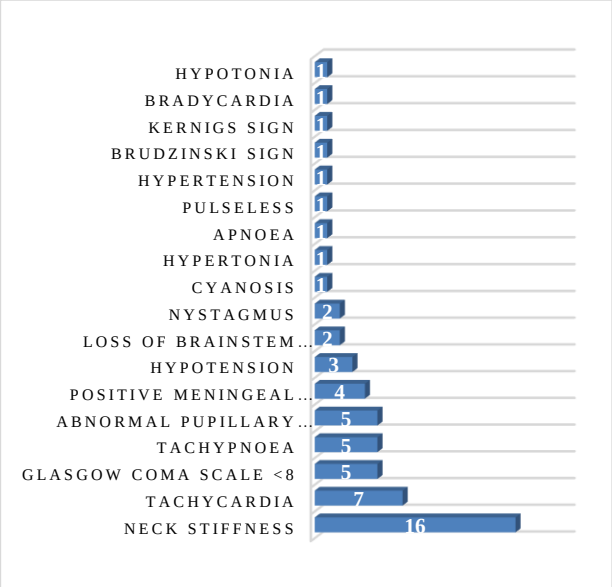

Figure 1: Examination findings.

Lab investigations

Laboratory findings of 17 cases were analysed and the cases with more leucocytes as well as neutrophils were also documented. Out of 17, 14 had elevated leucocytes, 13 had elevated neutrophils, 4 shows elevated CRP and 1 shows elevated lactate. Patients with number of elevated leucocytes is depicted in Table 5.

Findings in CSF analysis

CSF analysis of 30 documented cases were as follows and positive wet mount preparation was done in 28 patients (Table 6).

Radiological findings

Radiological findings of documented 17 cases were summarized in Table 7.

Other test

Other diagnostic test was done in some patients out of 45. 11 cases were diagnosed with polymerase chain reaction, 8 with next generation sequencing and 3 with metagenomic next generation sequencing

Associated diseases

Out of 45, 6 cases had other associated diseases. Thyromegaly, type II diabetes mellitus, acute leukaemic leukaemia, ebstein barr virus infection, extra pulmonary testicular TB and diabetes insipidus are the associated diseases with 1 patient in each.

Table 2: No. of cases according to age.

Age (In years)	No. of patients
0 to 9	7
10 to 19	13
20 to 29	6
30 to 39	5
40 to 49	7
50 to 59	4
60 to 69	2
70 to 79	1

Table 3: No. of cases according to history of exposure.

S. no.	Exposure	No.of patients
1	Swimming in natural lake	5
2	Recreational water activities	8
3	Nasal rinsing	4
4	Swimming pool	2
5	Canal swimming	2
6	Swimming in pond	2
7	Swimming in pond and irrigating nostrils	1
8	Artificial pool in home terrace	1
9	Splashed by waste water from old water pipe	1
10	Access to drainage ditches and canals	1
11	Contact with water (not specific)	4

Table 4: No. of cases according to symptoms.

S. no.	Clinical features	No. of patients
1	Fever	34
2	Headache	34
3	Vomiting	23
4	Altered sensorium	22
5	Fatigue	12
6	Seizures	10
7	Photophobia	7
8	Irrelevant talk	7
9	Coma	5
10	Nausea	4
11	Dizziness	3
12	Cough	3
13	Poor oral intake	3
14	Bodyache	2
15	Sore throat	2
16	Dyspnoea	2
17	Retention of urine	2
18	Skin rash	2
19	Sensation of ear pressure	1
20	Abdominal pain	1
21	Urinary incontinence	1
22	Loss of vision	1
23	Hearing loss	1
24	Difficulty in swallowing	1
25	Nasal congestion	1
26	Roving eye movements	1
27	Difficulty in walking	1
28	Earache	1
29	Phonophobia	1
30	Backache	1
31	Listlessness	1

Table 5: Patients with leucocytosis.

S. no	No. of leucocytes	No. of patients
1	10,001-15,000 cells	7
2	15,001-20,000 cells	5
3	20.001-25,000 cells	2
4	Elevated WBC	1

Day of death from appearance of symptoms

The day of death from appearance of symptoms ranges from 3 to 64 days (Table 8).

Place from where cases were reported

Death cases due to PAM documented from 1978 to 2024 were analysed and 15 cases were reported from India (Table 9).

Table 6: Abnormal findings in CSF analysis.

S. No	CSF findings	No. of patients
1	Increased WBC count	23
2	Increased neutrophils	15
3	Increased lymphocytes	2
4	Increased protein	21
5	Decreased glucose	13
6	Increased RBC count	10
7	Increased Intracranial pressure	10
8	Increased glucose	3
9	Decreased chloride	2
10	Increased LDH	1
11	Increased lactate	1

Table7: Radiological findings.

S. no.	Radiological findings	No. of patients
1	Cerebral oedema	13
2	Tonsilar/Uncal/Transtentorial herniation	7
3	Global sucal effacement	4
4	Signs of meningitis	3
5	Encephalitis	3
6	Foggy brain ventricles	3
7	Hydrocephalus	2
8	Posterior fossa mass effect	1
9	Leptomeningeal linear enhancement in occipital lobe	1

Table 8: Day of death from appearance of symptoms.

S. no.	Day of death from appearance of symptoms	No. of patients
1	3	3
2	4	7
3	5	4
4	6	4
5	7	5
6	8	4
7	10	1
8	11	3
9	14	1
10	16	1
11	17	1
12	18	1
13	20	1
14	24	1
15	25	1
16	45	1
17	64	1

Table 9: Place from cases were reported.

S. no.	Place	No. of patients
1	India	15
2	China	13
3	USA	12
4	Pakisthan	1
5	Australia	1
6	Nepal	1
7	Germany	1
8	Zambia	1

DISCUSSION

Details of 45 cases died from PAM were analysed and summarized. Out of 45 cases, 13 patients were between the age group 10 to 19 years. In a study reported in USA regarding the epidemiology of PAM in USA between 1962 and 2008, the median age of the cases was 12 years.27According to technical guidelines in diagnosis and prevention of PAM in Kerala, the most common age group suffering with PAM belongs to first three decades.1

Overall, the male to female ratio of PAM is 2:1.[1] In a epidemiological study conducted in USA, out of 111 cases males accounts for 88.[5] In the present review, out of 45 cases,42 (93%) were males.

Out of 45 cases, history of exposure is not documented in 10 cases. 4 had no history of exposure. All others had history of exposure to water before the infection. The infection occurs once the person gets contact with water contaminated by amoeba through nasal mucosa.[2] Epidemiological studies in USA shows that amoeba proliferate in natural bodies of water.[27] A mini review on *N. fowleri* suggests that the infection is common among persons engaged in recreational water activities.[4]

According to the present review, the duration from exposure to production of symptoms ranges from 3 days to a maximum of 1-2 months. The persons will produce symptoms within 1-9 days after exposure to water.[1] A review on Pathology of brain eating amoeba reports that,not later than 14 days after exposure, the symptoms appear.[2]

Clinical symptoms of the 41 cases out of 45 cases had been documented and analysed. Out of which most common presentations were fever, headache, vomiting and altered sensorium. The change in host immune response due to affection of trophozoite leads to inflammatory response in brain parenchyma leading to necrosis and damage of brain parenchyma.[1]

The most common presentations according to literature are severe headache, fever and chills, stiff neck with photophobia, nausea and vomiting, positive Brudzinski sign, positive Kernig sign, increased intracranial pressure and increased cerebrospinal fluid pressure has direct association with death.[4,29] Examination findings of 24 cases were analysed and presented with stiff neck, positive meningeal signs and other features which are in accordance with those in literature.

Regarding laboratory investigations, leukocytosis (300 to 26,000 cells/mm) with predominant polymorphonuclear cells, presence of red blood cells, elevated protein and low glucose during cerebrospinal fluid (CSF) examination are the characteristic finding in PAM. Fast moving *N. fowleri* trophozoites can be seen in wet mount preparation of CSF. PCR technique of CSF detects DNA of *N. fowleri*. Abnormalities in various structures of brain including subarachnoid space and midbrain can be identified in MRI of Brain.[1,4,29] Out of 17 patients having lab investigation, 14 had elevated leucocytes. In this article, 30 patients had CSF examination findings. Increased WBC count and increased protein were seen in 23 and 21 respectively. 13 patients presented with cerebral oedema in radiography. Postmortem finding of *N. fowleri* in brain tissue was found in 5 patients. Of the 45 patients, PCR was positive in 11, Next Generation Sequencing (NGS) in 8 and metagenomic next generation sequencing (mNGS) in 2 cases.

Regarding the day of death after appearance of symptoms, the range is from 3-64 days. Case fatality rate of PAM is more than 95% and death can occur in 3-7 days.[3] According to the article on PAM in MSD manual, the death will occur within 10 days of infection.[28]

The 45 death cases documented from 1978 to 2024 were included in the analysis. The demographic data, clinical symptoms, exposure, investigations and diagnosis were reviewed. As PAM is mostly a fatal disease and it mimics bacterial meningoencephalitis and difficult to diagnose, more extensive research should be carried out for generalization of results.

CONCLUSION

Out of 45 cases documented, most of the patients had contact with water contaminated by *N. fowleri* which shows the importance of decontamination of the water resources for preventing the spread of fatal disease. Late diagnosis of most of the cases due to resemblance of symptoms with bacterial meningitis is also a cause for lethality.

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