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PRIMARY AMOEBIC MENINGO-ENCEPHALITIS

by

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At the Fourth Conference (Nouméa, January 1973) of Directors of Pacific Territorial Health Services, Professor J.A.R. Miles was asked to prepare a paper on Primary Amoebic Meningo-Encephalitis, for publication and distribution by the South Pacific Commission.

Although no cases of this disease have yet been reported in the South Pacific, conditions are such that it might well be introduced sooner or later in one or other of the territories.

It is clearly of the utmost importance that territorial health personnel should be able to diagnose a case, if and when it should occur; the following short article has been written to enable them to do so.

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South Pacific Commission,
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(227/73)

Primary amoebic meningo-encephalitis is a highly fatal human disease which has only recently been recognised and whose importance has not yet been fully assessed. Between the first publication of an account of the disease in 1965 and the end of 1971, 69 possible cases were reported of which Carter (1972) regarded 57 as proven. Of these 10 were diagnosed in Australia, 27 in the Southern U.S.A., 4 in New Zealand, 17 in Czechoslovakia, 8 in Western Europe, 2 in India and one in Africa. The present reported distribution probably relates to the location of laboratories where the diagnosis is considered rather than to the true distribution of the condition and the frequency of its occurrence is quite unknown. All the reported cases except one have been fatal.

Clinical Features

Most patients were in robust health before the onset of the illness and in the great majority of cases a history can be obtained of swimming in warm fresh water, often including a lot of diving or under-water swimming, 3-10 days before the onset of illness. No cases have been reported following sea bathing.

The onset has been rapid with headache and mild fever, sometimes associated with rhinitis and/or sore throat, progressing through increasing headache, pyrexia, vomiting and neck rigidity to severe disorientation. By the third day some of the patients are comatose.

A diagnosis of acute meningitis is confirmed by the presence of a purulent C.S.F.

The table shows the variations in the laboratory findings on the C.S.F.

Investigation	Range of findings
Leucocytes cu/mm	400-20,000
% Polymorphs	75-100
Amoebae cu/mm	0-800
Erythrocytes cu/mm	0-5000
Protein mg per 100 ml	100-1000
Sugar mg per 100 ml	0-180
Chlorides mg per 100 ml	550-740

In general the C.S.F. picture is similar to that in bacterial meningitis except that in most cases there is less lowering of the sugar and that bacteria are neither seen nor cultured. When numerous amoebae are present they may be recognised in the counting chamber, but they are much more easily seen in a wet preparation examined either with reduced light or, preferably by phase contrast.

In most cases the disease progresses inexorably through deepening coma and rising intracranial pressure until the patient dies in cardio-respiratory failure on the fifth or sixth day.

Treatment with anti-bacterial and anti-amoebic drugs has had no effect on the progress of the disease, but there is evidence of a therapeutic effect of amphotericin B both experimentally and clinically and one patient treated with this drug has recovered (see below).

The causative organism

The responsible protozoan is a typical limax amoeba of the genus Naegleria and the responsible species has been named fowleri in honour of the pathologist at the Adelaide Children's Hospital who first described the disease in man.

The active trophozoite is a slug-like amoeba which moves by a single anterior pseudopod. The average size is 22 x 7 μ. 1-6 contractile vacuoles are usually readily seen, but the nucleus is difficult to see except in squash or stained preparations. The amoebae are active at all temperatures above 20°C and normally a warm stage is unnecessary for their study. They are damaged by refrigeration and destroyed by freezing or desiccation.

In a hanging drop preparation at 21°C they will remain healthy and active for up to 10 days. After about a day they transform to a biflagellate form without a cytostome and will swim round for several hours before returning to the amoeboid form.

Cysts, about 9μ in diameter form after 4 days in culture at 37°C. These are not resistant either to freezing or desiccation.

Culture

The simplest method of culturing this amoeba is on a lawn of living Escherichia coli on a nutrient agar plate. The colonies of amoebae can then be recognised macroscopically by areas from which the E.coli growth has been cleared. The amoeba will also grow in fluid medium containing E.coli killed at 60°C but not at 65°C. Cerva (1969) has reported that the Naegleria can be grown in a modified Korthof's medium.

Epidemiology and Pathogenesis

Naegleria spp. are soil organisms which are widespread in nature and may be found in moist soil and fresh water. Pathogenic Naegleria fowleri have not yet been isolated from such sources, but it is almost certain that their normal habitat is similar to that of the other species. These amoebae cannot survive in salt water.

Most cases occur in individuals who have been swimming underwater, or diving in warm, unfiltered, fresh water. All New Zealand cases have followed swimming in water originating in hot springs and at a temperature of 30°C or higher. No case has been recorded from a chlorinated swimming pool.

Some Australian cases have occurred in children who have not been swimming in fresh water. Carter has suggested that the source of infection was likely to have been domestic waste water or sewage tank effluent. The area from which they came is one where summer temperatures are high and opportunities for such exposure abound.

Experimental studies in mice have shown that the organisms spread directly from the nose to the brain and the epidemiology strongly suggests that the same happens in man. In mice a very few pathogenic amoebae can infect by the intra-nasal route. Carter has obtained infection with 39 organisms instilled in 20 cu.mm of water.

Treatment

Treatment with antibacterial or anti-amoebic drugs has proved totally ineffective. However the toxic anti-fungal drug Amphotericin B has been shown to be highly lethal to Naegleria in vitro and to protect mice from infection. The use of this drug in 6 human cases has been reported. In four there was no clinical response although the amoebae showed signs of drug damage; in one life was substantially prolonged and in the sixth the patient recovered and was discharged apparently well. I quote Carter's (1972) account of this case.

"..... The patient, a 14-year-old boy from Queensland, presented in October 1971 with typical acute symptoms and was already in the fourth day of the illness and comatose by the time amphotericin B treatment began. The diagnosis was confirmed beyond any doubt by finding 12,000 white cells per c.mm. and numerous amoebae in the cerebrospinal fluid; the amoebae were cultured and by all studies done to date appear to be identical with Naegleria fowleri. Amphotericin B was given in a dose of 1 mg./kg. per day intravenously and the penicillin, ampicillin and sulphadiazine he had been having for 3 days previously were continued. Within 2 days he had become afebrile and was talking rationally. After 5 days the cerebrospinal fluid white cell count had fallen to 15/c.mm. but many atypical amoebae were still present. Amphotericin B was therefore given intrathecally and later intraventricularly in small doses (0.1 mg. on alternate days) and the fluid gradually cleared. The patient has since been discharged from hospital apparently quite well.

There can hardly be any doubt that this patient would have died without treatment and that his survival was due to the amphotericin B and not the other drugs given. Nevertheless we believe that sulphadiazine should always be used as well in case the amoebae involved should occasionally prove to be Hartmannellids. These amoebae have actually been shown to be resistant to both drugs in vitro (Casemore, 1970; De Carneri, 1970), but there is good evidence that they are affected by sulphadiazine in vivo (Culbertson, Holmes and Overton, 1965). We also believe it is important not to use corticosteroids which may combine with amphotericin B (a sterol-binding drug) and thus reduce its effective concentration in the tissues (Mandal et al., 1970). ....."

Summary

A brief account of the occurrence and characteristics of primary amoebic meningo-encephalitis is given. Evidence is given that treatment with amphotericin B may be effective.

In view of the close association of this condition with high ambient temperatures and with under-water swimming in warm fresh water it appears probable that this condition will prove not to be rare in the tropics. It should always be considered when purulent C.S.F. from a case of acute meningitis fails to yield any bacteria and fails to respond to chemotherapy.

References

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