CRYPTOCOCCAL MENINGO-ENCEPHALITIS

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Introduction

Involvement of the central nervous system with Cryptococcus neoformans (Torula histolytica) is probably not as rare as was once supposed. Most reports of cases have emanated from the United States, where at least 50 deaths a year are attributed to cryptococcosis. There are reports of fewer cases in Great Britain and Australia, where the incidence is probably lower. From Malaya two cases only (Institute of Medical Research Annual Report 1953; Ross-Russell and Dean 1957) were reported up to 1959; since then, four more cases have been diagnosed (Lim Teong Wah and Chan Kok Ewe 1962).

An awareness of the disease is leading to the discovery of increasing numbers of cases, which is important because of the probably therapeutic value of AMPHOTERECIN B, the fungicide used in the treatment of this disease.

Case Report

A Gurkha soldier, aged 28, presented in India in April 1959 with a girdle-type pain at the twelfth intercostal level. X-ray examination of the spine was not carried out, but a chest X-ray film showed a patchy opacity at the left apex. His erythrocyte sedimentation rate was 40 mm. and acid-fast bacilli were isolated from his sputum. Treatment with streptomycin 1 G. and I.N.A.H. 200 mgm., daily, was commenced on 1st May, 1959, and the patient was transferred to a sanatorium in Malaya in October, 1959.

Within three months of the commencement of treatment his sputum became negative for acid-fast bacilli, his chest X-ray appearance had improved considerably and E.S.R. was 14 mm./hr. His pain had resolved. Thirteen months later, tomography revealed complete clearing of the left apical opacity and he was returned to his unit taking P.A.S. 15 G. and I.N.A.H. 200 mgm. daily. He had received 503 G. of streptomycin while an in-patient.

He remained well until February, 1961, when he was re-admitted to hospital complaining of a burning feeling behind his eyes, frontal headache, dizziness and occasional vomiting. His condition improved after a week, and although he was not eating well and had lost weight there was no abnormality on clinical examination, and no evidence of reactivation of tuberculosis. He was observed in hospital and was well until 13th March, when a lumbar puncture was performed on account of the fairly rapid onset of headache and neck stiffness associated with fever. The cerebrospinal fluid was clear, under normal pressure and contained protein 65 mgm. per cent, sugar 60 mgm. per cent, chlorides 740 mgm. per cent and cells 90/μl. mm. (Lymphocytes 88 per cent, polymorphonuclears 12 per cent). There was no growth on culture and no acid-fast bacilli were seen. At this time his haemoglobin was 15:1 G. (Haldane), white cells 5,500, normal differential count, E.S.R. 35 mm./hr. (Westergren), chest X-ray was normal and Heaf test positive Grade III.

During the next week, although his general condition deteriorated with increase in meningism, the striking feature was that he did not seem as ill as a patient with bacterial or viral meningitis. The dose of I.N.A.H. he was already taking for his pulmonary tuberculosis was increased to 600 mgm. daily, and streptomycin was given 1 G. intramuscularly and 100 mgm. intrathecally from 18th March, onwards.
**TABLE I**

Cerebrospinal Fluid

<table>
<thead>
<tr>
<th>Date</th>
<th>Appearance</th>
<th>Protein mgm.</th>
<th>Sugar mgm.</th>
<th>Total cells per cu. mm.</th>
<th>Polymorphs. per cent</th>
<th>Lymphocytes per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>14/3/61</td>
<td>Clear</td>
<td>65</td>
<td>60</td>
<td>90</td>
<td>12</td>
<td>88</td>
</tr>
<tr>
<td>15/3/61</td>
<td>Clear</td>
<td>60</td>
<td>65</td>
<td>70</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>20/3/61</td>
<td>Straw-coloured</td>
<td>125</td>
<td>75</td>
<td>60</td>
<td>8</td>
<td>92</td>
</tr>
<tr>
<td>27/3/61</td>
<td>&quot; &quot;</td>
<td>80</td>
<td>60</td>
<td>&quot; &quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>31/3/61</td>
<td>&quot; &quot;</td>
<td>65</td>
<td>70</td>
<td>35</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>9/4/61</td>
<td>&quot; &quot;</td>
<td>200</td>
<td>20</td>
<td>120</td>
<td>54</td>
<td>46</td>
</tr>
<tr>
<td>11/4/61</td>
<td>&quot; &quot;</td>
<td>180</td>
<td>20</td>
<td>205</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>13/4/61</td>
<td>&quot; &quot;</td>
<td>150</td>
<td>15</td>
<td>200</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
<tr>
<td>20/4/61</td>
<td>&quot; &quot;</td>
<td>120</td>
<td>35</td>
<td>205</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>25/4/61</td>
<td>&quot; &quot;</td>
<td>100</td>
<td>40</td>
<td>&quot;</td>
<td>&quot;</td>
<td>&quot;</td>
</tr>
</tbody>
</table>

Cryptococci seen.
Gradual deterioration continued, although he improved for a short time when ethionamide was given, and again when hydrocortisone 100 mgm. and streptomycin 100 mgm. intrathecally were given on alternate days, in place of the daily intrathecal streptomycin. The improvement lasted two weeks during which time he started to gain weight and was apyrexial. On 25th April, headache returned, neck rigidity increased and a positive Kernig's sign was demonstrable. The outline of the left optic disc became blurred and for the first time the cerebrospinal fluid pressure was elevated above normal. On this day Cryptococcus neoformans was first isolated from the cerebrospinal fluid on direct smear (Indian ink preparation) and later cultured on Sabouraud's medium and identified by intracerebral inoculation of mice.

Anti-tuberculous therapy was discontinued and amphotericin B started intravenously (11.5 mgm. in 5 per cent glucose daily). Administration was made difficult by acute exacerbation of headache and vomiting while the intravenous fluid was being given, although salicylates and antihistamines were given at the same time. During the third day of this treatment he had a rigor and became incoherent for a short period, his blood pressure rising to 190/130 mm. (previously 125/80) and he developed oliguria. On the following day bilateral papilloedema and a left sixth cranial nerve palsy developed. He began to expectorate large quantities of mucoid sputum and bilateral rales were present in the chest. He was treated with tetracycline but gradually became comatose and died one week after the start of amphotericin therapy.

At autopsy there was evidence of bronchopneumonia. A puckered scar was seen in the left upper lobe of the lung with a surrounding area of emphysema. The meninges appeared congested and opaque with a few localized submeningeal purulent areas. The convolutions of the brain were flattened and the vessels congested, the brain substance being edematous and soft. There were several small jelly-like areas on the surface of the brain from which Cryptococcus neoformans was obtained, seen on direct smear and cultured. Throughout, the brain were scattered petechial hemorrhages. The left ventricle of the brain was dilated. In the abdomen there was no free fluid but the greater omentum was converted into a pus-containing loculated sac in the left iliac fossa. There was no growth on ordinary media or Sabouraud's medium from this pus, and cryptococcus could not be demonstrated on smear. Unfortunately the histological specimens of the brain were destroyed.

**Discussion**

*Cryptococcus neoformans* is found in soil and particularly in pigeon droppings. The portal of entry of the fungus into the body is obscure but most observers believe it to be the lungs or skin. Pulmonary lesions are usually seen as "coin" lesions, as a miliary picture or an infiltrating type resembling viral pneumonia (Durant et al. 1960). In the case described the initial pulmonary lesion was undoubtedly tuberculous in view of the positive sputum, but it is conceivable that the cryptococcus gained entry at this time. Many reports describe cryptococcal infection in association with other diseases, such as Hodgkin's and other malignant conditions (Gendel et al. 1950, Zimmerman and Rappaport 1954, Smith, 1960). Cases with coexistent tuberculosis have also been reported (Wolfe and Jacobson 1958, Nichols and Martin 1955) and it has been suggested that isoniazid might enhance the growth of *Cryptococcus neoformans* (Littman and Zimmerman 1956). It seems that a lowering of body resistance from another disease may allow the fungus to disseminate and propagate.

The clinical picture of central nervous involvement is not unlike that of tuberculous meningitis but with, sometimes, a tendency to remissions and exacerbations. Alternatively, a picture similar to that of a cerebral tumour may develop. Cerebrospinal fluid shows increase in the number of white cells usually 300–700 per cu. mm., lymphocytes predominating. Protein is raised and sugar and chloride levels low. The characteristic organism is thickly encapsulated and best demonstrated in an Indian ink preparation.
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ink preparation (see plate). Budding is often seen. The cryptococcus grows well on Sabouraud's medium forming creamy colonies. Intracerebral inoculation of mice with 0.05–0.1 ml. of infected cerebrospinal fluid kills the animals in three weeks, and smears of the brain tissue of inoculated mice show cryptococci as early as two days after injection (Lim Teong Wah and Chan Kok Ewe 1962). A haemagglutination test has been described (Pollock and Ward 1962) but is not yet of proved value.

Treatment with amphotericin B has been thought to be effective in many cases (Appelbaum and Shtokalko 1957, FitzPatrick et al. 1958, Durant et al. 1960). The drug is given intravenously in small initial doses, the chief side effects being nausea, fever, vomiting and thrombophlebitis. A transient rise in blood urea is often noted and renal and hepatic complications may ensue. In the case described the treatment was probably started too late to be of therapeutic value, the oliguria and elevation of systemic blood pressure may have been connected with the drug treatment.

Conclusion

Now that a therapeutic weapon is available the importance of early diagnosis of cryptococcal infection of the central nervous system has become of great importance. Cryptococci in the cerebrospinal fluid may be easily mistaken for lymphocytes unless special staining and culture methods are used. A clinical awareness of this disease should lead to the diagnosis of more cases.

ACKNOWLEDGMENTS

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REFERENCES