TWO JOURNEYS THROUGH TUBERCULOUS MENINGITIS

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Meningitis is the most challenging form of tuberculosis: whether it is a question of timely diagnosis, managing the illness or what to do if things go wrong during treatment, the problems for the physician are great and the hazards for the patient greater. This paper discusses the course of tuberculous meningitis (TBM) from the viewpoint of both the patient and the doctor.

THE PATIENT'S JOURNEY

The patient's journey begins, of course, with primary infection, unrecognised as it often is and therefore untreated. Blood-borne spread of the organism takes it to the brain. The celebrated pathological studies published by Rich[1] appeared to demonstrate that the first step was the establishment of a subcortical focus of infection which gradually enlarged until it reached the surface of the brain and discharged into the subarachnoid space. However, modern imaging methods suggest that this is not always the case and that the meninges themselves can be the first site of involvement of the central nervous system. Rarely, the meninges are involved by direct extension from an infection in bone.

The greatest danger of meningitis comes in the first year after primary infection and the risk is largest in the youngest children. But in the UK, most cases of TBM are in adults where its time relationship with primary infection is often difficult to discern and probably remote. About a quarter of patients with TBM also have miliary disease.

As in many forms of tuberculosis, the distinctive clinical feature is tempo. Most patients experience a gradual onset of symptoms, which include listlessness, anorexia, headache, vomiting and fever. A variety of other complaints such as abdominal pain, constipation, backache and cough may further cloud the issue. A history of several weeks of poor health is not uncommon; during this time there may periods of a day or two when the patient feels better and appears to be recovering. By contrast some patients with TBM present with less than a week's history of illness, perhaps because of the rupture of a subcortical focus of infection into the subarachnoid space.

As the disease gathers momentum, headache and vomiting come to dominate the clinical picture and the patient will begin to suffer neurological symptoms beyond those that merely reflect meningeal irritation. The accumulation of oedematous inflammatory exudate in the subarachnoid space can hamper the circulation or re-absorption of the cerebrospinal fluid leading to hydrocephalus which may be obstructive or communicating. The same process may surround and compress cranial nerves as they leave the brain, or the motor and sensory nerve roots as they leave the spinal cord. This disturbance of consciousness and focal nerve damage may be added to by signs that result from cerebral infarction caused by tuberculous endarteritis affecting the vessels passing through infected areas. The onset of cerebrovascular complications may be accompanied by fits. Added to these neurological problems there may be electrolyte disturbance caused by persistent vomiting and by inappropriate antidiuretic hormone (ADH) secretion. Before the era of chemotherapy, TBM was always fatal.

With treatment, however, the prospects are good - at least so far as relieving the systemic symptoms and preventing further neurological damage are concerned. Of course, this does not happen immediately and it is not unusual for new neurological signs, including those of hydrocephalus, to appear over several weeks after the start of treatment. Thereafter, the course is generally one of gradual improvement, though in some cases late problems including the appearance or enlargement of tuberculoma of the brain may cause complications. The neurological damage resulting from nerve entrapment in inflammatory exudate usually recovers, though sometimes the process of healing leaves a chronic fibrous arachnoiditis with permanent loss of function of nerves and nerve roots embedded in the subarachnoid space.

In general, the outcome depends on the severity of neurological damage at the time treatment is started: where there is none, almost all patients recover fully but among those who are comatose or hemiplegic, the mortality is high, and many are left with permanent damage. The prognosis is poorest in young children and the elderly.[2]

THE DOCTOR'S JOURNEY

Timely diagnosis

Tuberculous meningitis is now so rare in the UK (less than 100 cases a year in all age groups) that few physicians see the condition with any frequency. There are two requirements for correct diagnosis: the first is the recognition that the patient has meningitis and the second is the determination that the meningitis is caused by tuberculosis. Epidemiological study can give us some assistance. All forms of tuberculosis are commoner in almost every immigrant group to the UK, especially those from South Asia, and TBM should always be an early consideration in such patients with possible symptoms. Moreover, in young patients with TBM there is very often a history of recent contact with tuberculosis. Any information that such patients have already been screened for infection and declared normal should deliberately be set aside if they then present with illness.

All physicians know the symptoms of meningitis and how, in TBM, these are likely to be protracted. The problem is to unite this knowledge with a rare eventuality in most physicians' experience. A combination of fever and headache should always prompt the suspicion of meningitis of any form, and the more severe these symptoms, the more prolonged and the more associated with neck stiffness, photophobia and vomiting, the more they should call for examination of the cerebrospinal fluid (CSF). If the patient is a young child, the headache may be less obvious but signs of listlessness, anorexia and weight loss may be more.

In the elderly, the main signs may be confusion or a reduced level of consciousness. If there are also signs of raised intracranial pressure or of focal neurological damage, or if there is evidence of a possible source of a pyogenic brain abscess, a CT or MRI head scan should be done first. Otherwise the patient should have a lumbar puncture immediately.

Interpreting the CSF findings

The characteristic abnormality of the CSF in TBM is a lymphocytic pleocytosis, a high protein, a low glucose and *M. tuberculosis* seen as acid-fast bacilli on direct smear and grown on culture. But none of these abnormalities is constantly present for there are some cases with predominance of polymorph neutrophils, or even with a normal CSF cell count, in the early stage; both glucose and protein levels may also be normal. Even after culture of the CSF only 70% of samples are ultimately positive for *M. tuberculosis* in cases where the diagnosis is considered highly likely on other grounds.

So the main problem is how to handle lymphocytic meningitis. If CSF lymphocytosis is the only abnormality and the history of illness is no more than a week, the patient probably has viral meningitis. In the absence of any other evidence of tuberculosis, it is reasonable to await developments. If the symptoms persist for more than two days, another examination of the CSF should be performed and the whole situation should be reviewed. Textbook accounts of other causes of lymphocytic meningitis usually include partly treated pyogenic meningitis, sarcoidosis and malignant infiltration of the meninges. All of these should take a poor second place to TBM. Many patients with pyogenic meningitis have already received oral antibiotic treatment before admission to hospital, yet it is very rare for the CSF not to show a polymorph predominance in patients who are still clearly ill. Meningitis caused by sarcoidosis is even rarer than TBM in most populations and malignant meningitis is most unusual where the primary site of malignancy (usually breast or haematological disease) is not already well-known.

Can other investigations help?

Tuberculin testing should be done. The Mantoux method is best, for its result can be inferred after 48 hours. The test should use 10 T.U. (0.1ml of 1:1000 Tuberculin given intra-dermally). A reaction of >5 mm induration is significant in patients who have not received BCG. If the patient has previously had BCG the interpretation of the Mantoux test is more difficult but a reaction of more than 15 mm induration is probably significant of tuberculous infection. A negative tuberculin test is not helpful.

A chest X-ray should be taken. The most significant abnormality is diffuse micronodular infiltration typical of miliary tuberculosis, but any other abnormality typical of tuberculosis, such as primary disease or post-primary pulmonary tuberculosis, is highly relevant.

In patients with a chest X-ray abnormality suggestive of tuberculosis, bacteriological examination of the sputum should be carried out. If there is no sputum, the possibility of recovering pulmonary secretions by lavage at bronchoscopy should be seriously considered. In patients with X-ray evidence of miliary tuberculosis, urine should be sent for culture as this is usually a reliable way of recovering the organism.

About half of patients with TBM have hyponatraemia at the time of diagnosis. Measuring the plasma electrolytes will allow this abnormality, caused by inappropriate ADH secretion, to be recognised.

Where are we now?

The patient has sub-acute meningitis and lymphocytic CSF. Unless an alternative diagnosis can be made with certainty a combination treatment for tuberculosis should be started. Four drugs should be given initially with isoniazid, rifampicin, pyrazinamide and either streptomycin or ethambutol being the first choice. They should be used in standard dosage and, if intestinal absorption is uncertain, isoniazid, rifampicin and streptomycin may all be given by injection. The addition of corticosteroids improves the outcome of patients with neurological damage: dexamethasone, in an adult dose of 8-12 mg/day tapered over six to eight weeks, has been used successfully for this purpose. The objection that steroids may reduce the permeability of the blood-brain barrier to antibiotics and hamper eradication of the infection seems to be theoretical. So long as the first choice antibiotics can be used, there seems to be no extra benefit from giving additional intrathecal or intraventricular treatment. Measures to counteract the effects of inappropriate ADH secretion may also be needed.

In many cases the above treatment is all that is required. The conventional pattern of management for other forms of tuberculosis can be followed, reducing the drugs to isoniazid and rifampicin after two months if the organism is sensitive. There is less certainty about the duration of treatment - many physicians cautiously extend the course to a total of nine or twelve months. Repeated sampling of the CSF is not needed if the diagnosis is secure and progress is good. If the organism has not been isolated from the patient then, unless the patient is part of a known outbreak, its drug sensitivity cannot be known. In these cases it is necessary to judge the likelihood of drug resistance by considering the background of the patient and their progress on treatment so far.

Some patients do badly on treatment and it is almost always necessary to repeat the imaging of the brain by CT or MRI scanning and to repeat the examination of the CSF. Some fluctuation of the CSF findings can be expected in the early stage of the disease, but a rising protein level may be a sign of impending spinal block and is a reason for starting steroids if they are not already being used. Imaging of the brain may reveal infarction caused by endarteritis, hydrocephalus, or the presence or enlargement of a cerebral tuberculoma. There is little else to be done about infarction, and tuberculomas are all best left alone if possible. However, hydrocephalus sufficient to aggravate symptoms should be discussed with a neurosurgeon. If the hydrocephalus is communicating, the removal of a substantial amount of CSF by lumbar puncture may give some idea of how much it is contributing to the patient's condition. Surgical relief of the hydrocephalus with a ventriculo-atrial or ventriculo-peritoneal shunt should be considered though, where the CSF protein is very high, there is a serious risk that the shunt will become blocked. In these cases a ventricular drain may be a better option.

At the other end of the spectrum is the patient who has been started, correctly, on anti-tuberculosis treatment for lymphocytic meningitis but in whom the diagnosis of tuberculosis soon seems unlikely. The best approach in

such cases, if no definite diagnosis can be made, is to repeat the examination of the CSF after one or two weeks. The CSF in TBM remains abnormal for months, even beyond the completion of satisfactory treatment in some cases. If within one or two weeks the patient's CSF is normal and there is no other evidence in favour of tuberculosis, the diagnosis of TBM can be abandoned and treatment stopped.

REFERENCES

1 Rich AR. *The Pathogenesis of Tuberculosis*. 2nd ed. Oxford: Blackwell Science; 1951.

2 Kent SJ, Crowe SM, Yung A *et al*. Tuberculous meningitis: a 30-year review. *Clin Infect Dis* 1993; 17:987-94.

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