

## Tuberculous meningitis

Tuberculosis is the world's leading cause of death from a single infectious agent. It is on the increase not only in underdeveloped countries but in the developed world too with a 30% increase in the number of cases in Switzerland in the four years up to 1990 and a 25% increase in Italy between 1988 and 1990.<sup>1</sup> In Britain no increase is reported yet but the decline noticed in the 1980s has now stopped; 7000 cases are reported each year. Multiple drug resistance, inadequate disease control programmes, and the advent of HIV infection all contribute to the current picture.

In 1985, 5% of 4000 extrapulmonary cases of tuberculosis in the USA were due to tuberculous meningitis.<sup>2</sup> Whereas non-osseous tuberculosis affecting the central nervous system may take a number of different forms including discrete large tuberculomata acting as space occupying lesions and more rarely myeloradiculopathy, tuberculous meningitis remains the most common threat to health.

Outcome in tuberculous meningitis is strongly associated with the stage of disease at presentation. Disease staging was first proposed by the Medical Research Council in 1948<sup>3</sup>: stage I=conscious, non-specific symptoms and no neurological signs; stage II=a degree of mental confusion and emerging neurological signs; stage III=these children are extremely ill with deepening coma often accompanied by the evolution of focal neurological signs. The incidence of residual neurological handicap or death rises steeply where appropriate treatment is not initiated until after the emergence of reduced conscious level and focal neurological signs.

Recently, Humphries *et al* reported on outcome in 1990 Chinese children with tuberculous meningitis treated in Hong Kong between 1961 and 1984,<sup>4</sup> and Schoeman reported on a prospective epidemiological study of 75 with tuberculous meningitis in Bloemfontein.<sup>5</sup> Their findings correspond to those of many other authors.<sup>2 6 7</sup> Complete recovery was the rule in stage I cases, but was seen in only about 20% in stage III. None died in stage I whereas up to 23% died in stage III. A third in stage III retained severe disability. Both studies showed that younger children were less likely to make a full recovery than older children. In the South African study 55% aged 12 months or less had a poor outcome compared with good recovery in all those aged 10 years or more.

These findings serve to emphasise that early recognition of tuberculous meningitis with early treatment, particularly in young children, is of paramount importance to optimum outcome. None the less, significant delays are still seen from time to time. In my experience, the delay seems to result not from clinicians failing to think of tuberculous meningitis but in their interpretation of investigations. Clinicians often prefer to interpret cerebrospinal fluid findings as representing a viral meningitis requiring no specific treatment. It may be they are reticent to commit themselves to 12 months of potentially toxic therapy. The resulting expectant policy brings appropriate intervention only after there has been a significant deterioration in the child's condition.

This annotation should serve to evaluate and re-emphasise the key factors in a child's presentation with tuberculous meningitis and the therapeutic options.

### History and signs

It is very unusual for tuberculous meningitis to present acutely; there is more often than not a subacute presenta-

tion over a number of weeks or even months. Invariably a focus of infection lies elsewhere (usually in the lungs) and bacteria reach the central nervous system by haematogenous spread or more rarely local extension. Retrospective studies suggest that at least 75% of individuals have such an infection at least 12 months before presentation.<sup>8</sup> Jensen *et al*,<sup>7</sup> studying tuberculous meningitis in 23 patients of all ages (five under 10 years) showed the duration of symptoms ranges from two–180 days: a median of 14 days, two shorter than that reported in Illingworth's 1950 paper.<sup>9</sup>

Prodromal symptoms most commonly include vague features such as lassitude, pallor, anorexia, weight loss, cough, and night sweats followed by the emergence of symptoms attributable to the central nervous system notably headache (worse in recumbancy), pain and neck stiffness, and then finally and more dramatically stupor, seizures, deterioration in conscious level, and the emergence of focal signs. There is often a history of active infection in another family member or recent travel to an area where the disease is endemic.

Clinical signs that may be helpful or suggestive of tuberculous meningitis include evidence of weight loss, adenopathy which is more commonly cervical, adventitious sounds in the lungs, particularly in the apices, choroidal tubercles, irregular fever at its height in the late afternoon, nuchal rigidity or a full 'boggy' fontanelle. Absence of these signs by no means excludes the diagnosis. In Illingworth's classical 1956 paper on his experience with 256 children, only 25% had meningism, 11% choroidal tubercles (where the chest radiograph was normal), and 40% papilloedema.<sup>10</sup>

### Special investigations

About half of children with tuberculous meningitis have abnormalities on the chest radiograph<sup>4 11</sup> including signs of a primary complex, miliary shadowing, parenchymal change, mediastinal glands, and pleural effusion. Where chest radiography findings are seen with an aseptic meningitis the diagnosis is tuberculosis until proved otherwise.

The most useful guide to diagnosis is found in the cerebrospinal fluid. The cardinal features of tuberculous meningitis are of a low cerebrospinal fluid glucose<sup>4 7 11</sup> (less than 50% of the serum concentration) and of a raised protein concentration<sup>4 7 10</sup> (often 1.0–3.0 g/l). Protein concentrations as high as this are very rare in other bacterial meningitis outside the neonatal period. The cerebrospinal fluid glucose is only very rarely extremely low as often seen in a pneumococcal or meningococcal infection. Illingworth emphasised this point and that absolute values may be normal<sup>10</sup>; it is essential to measure the plasma glucose at the same time as the cerebrospinal fluid glucose to allow sensible interpretation of the results.

The cellular response in cerebrospinal fluid usually shows pleocytosis of less than  $500 \times 10^6/l$ . Polymorphonuclear cells predominate initially with lymphocytes being more prevalent after 48 hours or so. The mean white cell count in blood is about  $260 \times 10^9/l$ ,<sup>4</sup> about one in 40 will have a count greater than  $1000 \times 10^9/l$ .

The acid fast bacilli themselves may be very difficult to identify even on centrifuged cerebrospinal fluid. Molavi and LeFrock in a series review commented that mycobacteria were identified in only 10–40% and by culture in 45–90%.<sup>6</sup> Repeat examinations taking as much cerebro-

spinal fluid as possible increased the yield on direct microscopy to as high as 87%.

Mantoux testing with purified protein derivative of *Mycobacterium tuberculosis* is on the whole unhelpful with perhaps only 25% proving positive in the face of active tuberculous meningitis. Clinically, there is the additional disadvantage of at least a 48 hour wait until a result is evident, but it must be remembered that early treatment does not alter skin test reactivity.

Laboratory methods are available for the rapid detection of tuberculous meningitis. In the past adenosine deaminase, radioactive bromide partition testing, and quantification of mycobacterial metabolites such as 3-(2'-keto-hexyl)-indoline were proved not to be satisfactory or to have low specificity.<sup>12 13</sup> An enzyme linked immunosorbent assay (ELISA) using BCG antigens does have high specificity (95%) and sensitivity (81%)<sup>14 15</sup> but the methods are complex and more suitable for research rather than routine clinical work. A latex agglutination technique showed higher specificity,<sup>16</sup> but technical problems with sensitivity have hampered its development for widespread use.

Detection of specific DNA sequences of *M tuberculosis* in specimens by use of labelled 'DNA probes' is rather insensitive, although the sensitivity may be increased greatly by the use of the polymerase chain reaction (PCR) amplifying small amounts of the specific DNA. PCR has proved to be a sensitive technique detecting 15 (75%) of 20 cases of highly probable tuberculous meningitis.<sup>17</sup> As the method is capable of detecting the tiniest amount of specific DNA false positive results are common unless laboratory methods stringently prevent cross contamination.

Where ambiguity still exists despite all the special investigations, the clinician must be prepared to have the courage to 'treat the treatable' where the clinical context is compelling.

### Drug treatment

There is currently no general consensus about the form of chemotherapy or optimal duration of treatment. Currently eight antituberculous therapeutic agents are available (isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, ethionamide, and cycloserine). All except streptomycin have good penetration into the cerebrospinal fluid and intrathecal treatment is no longer indicated. Kanamycin and ethionamide have a high frequency of unacceptable side effects and should be reserved for first line drug failure.

The Centers for Disease Control recommend that treatment is started with isoniazid (10–20 mg/kg/day up to 300 mg), rifampicin (10–20 mg/kg/day up to 600 mg), and pyrazinamide (15–30 mg/kg/day up to 2 g per day).<sup>18</sup> Children should be monitored for hepatotoxicity from the rifampicin which is seen in about 20% of cases; its emergence would lead to seeking an alternative agent.

Ethambutol or streptomycin may be added if there is an initial poor response and if drug resistance or adverse reactions emerge then ethionamide, kanamycin, or ciprofloxacin may be added. Advice from a consultant microbiologist specialising in infectious diseases should be sought at this stage.

The British Thoracic Society recommends isoniazid, rifampicin, and pyrazinamide for a two month period followed by isoniazid and rifampicin for a further 10 months.<sup>19</sup> The American Academy of Pediatrics recommends the additional use of streptomycin for the first two month period.<sup>20</sup> The author's practice is to omit streptomycin.

Some advocate the administration of 25–50 mg/day of pyridoxine to prevent peripheral neuropathy when isoniazid is administered but the author has never encountered this in British children on an adequate diet. Its use should be reserved for breast fed infants, the malnourished, and rapidly growing adolescents.

Steroids have not been used routinely but are reserved for the event of clinical deterioration after the administration of treatment. In these circumstances, prednisolone 2 mg/kg/day has been prescribed or when there are signs of raised intracranial pressure (stages II and III). The drug should be continued for four to six weeks and tailed over a further two to three weeks. Steroids do not lessen the penetration of drugs into the cerebrospinal fluid.<sup>21</sup> Given current thoughts on the use of steroids in meningitis they should probably be advocated for all children with tuberculous meningitis.

A number of studies report varying experience with short course treatment (periods as short as six months).<sup>22–24</sup> As recrudescence of tuberculous meningitis with the emergence of neurological deficit is seen in some of these studies a minimum of 12 months' treatment should continue to be advocated.

Immanuel and colleagues related the erythrocyte sedimentation rate and acute phase proteins to the effect of treatment.<sup>25</sup> Only  $\alpha_1$  acid glycoprotein seemed to mirror disease activity with its concentration raised in 90% of patients with pulmonary tuberculosis and admission and in only one of 20 patients at the end of treatment. Measurement of these proteins is unlikely to replace clinical acumen and empiricism.

### Computed tomography

A computed tomogram in tuberculous meningitis may reveal basilar enhancement, hydrocephalus, local infarction, or tuberculomata. Routine scanning is not indicated if the diagnosis is evident from the cerebrospinal fluid findings. The scan findings may clarify the diagnosis if cerebrospinal fluid findings are equivocal. Where there is a deterioration in the clinical condition and in particular the emergence of coma, scanning is indicated looking particularly for the emergence of hydrocephalus.

### BCG vaccine

BCG vaccine appears to lower the risk of serious complications of pulmonary tuberculosis with the Centers for Disease Control reporting incidence of miliary and tuberculous meningitis reduced to 52–100% lower in vaccinated children.<sup>26</sup> However, in a number of studies about half those with tuberculous meningitis have received BCG vaccine with no difference in survival rate.

### Neurosurgical intervention

Palur and colleagues advocate the early shunting of patients with tuberculous meningitis who have stage I and II disease with evidence of hydrocephalus on computed tomography.<sup>27</sup> Some dilatation of the ventricles is common in all cases and as an isolated finding on computed tomography it should not be regarded as an indication for shunting. Deteriorating neurological symptoms and signs seen in association with hydrocephalus is an indication to shunt. Young people with stage III disease are probably best treated by external ventricular drainage initially which allows better control of intracranial pressure. As the protein concentration falls secondary shunting can then be effected.

In April this year, the World Health Organisation took what it called the extraordinary step of declaring tuberculosis a 'global emergency'. In the light of the significant increase from reported cases worldwide, British paediatricians can play their part in controlling the disease by having a high index of suspicion for the diagnosis. As Illingworth wrote in 1950 ... 'when the ... doctor has good reason to suspect the diagnosis ... send the child ... without delay ... [for] ... the great advantage of early treatment'.<sup>9</sup>

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