Chapter 9
Tuberculous Encephalitis

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9.1 Context

Tuberculosis is an infection with multiple localizations, the most frequent being the lung. From this initial infection, bacteria spread in the body via the blood, acting as a bacteremia. Infectious metastases are various, and among them, brain is potentially the most severe.

It is difficult to differentiate encephalitis and meningitis, as they are most frequently combined. One could say that the importance of central nervous system symptoms is in favor of encephalitis rather than meningitis. A definition of encephalitis was published, in order to allow comparisons between studies at an international level [1]:

- A major criterion is required: the patient should present with altered mental status (defined as decreased or altered level of consciousness, lethargy, or personality change) lasting ≥24 h with no alternative cause identified.
- Minor criteria are required—two for possible encephalitis and three or more for probable or confirmed encephalitis:
  - Documented fever ≥38 °C (100.4 °F) within the 72 h before or after presentation
  - Generalized or partial seizures not fully attributable to a preexisting seizure disorder
  - New onset of focal neurologic findings
  - CSF WBC count ≥5/cubic mm

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- Abnormality of brain parenchyma on neuroimaging suggestive of encephalitis that is either new from prior studies or appears acute in onset
- Abnormality on electroencephalography that is consistent with encephalitis and not attributable to another cause

9.2 Epidemiology

From 2003 to 2014, 564,916 tuberculosis cases were reported by 27 EU/EEA countries, 83% presenting with exclusive pulmonary infection and 17% with extrapulmonary disease. Neurological involvement was reported as 3% of extrapulmonary infections [2].

In France, a study about 253 infectious encephalitis [3] reported 20 tuberculous encephalitis cases (5% of all cases, 15% of identified cases), sorted as confirmed (60%), probable (20%), and possible (20%).

The refugee crisis is mixing populations. A Spanish study, from 2004 to 2013, reported that, among 2426 immigrants, 2.85% of sub-Saharan patients presented with extrapulmonary tuberculosis, as well as 11% of patients coming from Maghreb, 4.4% of patients coming from Eastern Europe, and 1.5% of patients coming from Latin America [4].

In two European studies, one in France [5] and the other one in UK [6], tuberculosis appeared to be 15% of encephalitis with an aetiological diagnosis (8% of all cases including non-identified cases) and 12% of demonstrated infectious encephalitis, respectively. In the French study, neurotuberculosis was identified in patients who most likely had ancient infections but recent clinical resurgence. In the California Encephalitis Project, tuberculosis accounted for less than 1% of enrolled cases [7]. These discrepancies are related to the local epidemiology of tuberculosis.

9.3 Pathophysiology

The brain is colonized via a bacteremia, the primary infection being located in the respiratory tract, with or without symptoms. A small number of bacilli enter the bloodstream and spread throughout the entire body. The brain is one of the possible organs for metastasis.

In the brain, *Mycobacterium tuberculosis* acts like in the lung [8–10].

1. Three cell types are essential for protecting from *M. tuberculosis:*
   - Macrophages, phagocytizing bacteria. When ingested by macrophage, *M. tuberculosis* is located in phagosome. Then its urease stops acidification, so it prevents bacilli to be digested in the cell. In phagosome, antigens are presented to the class II major histocompatibility complex and stimulate CD4+ T

cells. As antigens don't diffuse into cytoplasm, they are not presented to class I major histocompatibility complex and by the way don't stimulate CD8+ T cells.
- CD4+ T lymphocytes secreting cytokines TH1 (IFN-alpha).
- CD8+ T lymphocytes secreting IFN-alpha able to lyse infected macrophages.

2. Granuloma is made by:
   - In its center, macrophages leading to multinucleated giant cells
   - In periphery, T and B lymphocytes

Necrosis can occur in the center, leading to caseous abscess, able to calcify or to liquefy.

The delay between primary infection and neurological presentation varies from some weeks (acute infection) to years (resurgence).

9.4 Anatomopathology

- The meningeal exudate characteristics are:
  - Most frequent and important in the brain base
  - Surrounding cranial nerve origins
  - Invading choroid plexus
  - May spread to ventricles, lobes
- Inflammation and necrosis are probably related to hypersensitivity reaction.
- Vascular lesions are correlated to the magnitude of meningeal lesions and may lead to fibrinous necrosis as well as thrombosis.

9.5 Clinical Presentation

Encephalitis is defined according the international definition [1], described above.

Typically, patients with neurotuberculosis present with some specific symptoms or circumstances. Delay for diagnosis has to be considered, most frequently related to the mild initial neurological presentation of a lot of cases, when compared with other infectious encephalitis. In a study reporting patients managed in France [3], the median delay between the onset of general and neurological symptoms was significantly longer for tuberculosis cases than for other encephalitis (10 days vs. 2; $P < 10^{-10}$). In this study only 20% of patients had a history of previous tuberculosis. None was associated with an ongoing tuberculous pneumonia. Eleven (55%) patients had stayed in the ICU, 10 of whom with mechanical ventilation.

9.6 Biological Features

9.6.1 CSF

Protein level in CSF is higher in tuberculosis patients than in other aetiologies [3]. The median CSF protein level was significantly higher for tuberculosis cases than for other encephalitis cases (2.1 g/L vs. 0.8 g/L, $P = 0.002$). The median pleocytosis was 150 cells/mm3 (range 4–640 cell/mm3). The glycorrhachia/glycemia ratio was low for 16/18 (89%) patients.

Diagnostic test sensitivity data reported are extrapolated from published data on tuberculous meningitis, because very few studies have been performed on encephalitis [11].

A prospective study of 132 tuberculous meningitis adult patients was performed in Vietnam in 2004. Authors obtained a microbiological diagnosis for 82% of patients. The microscopic examination and CSF cultures were positive for 58 and 71% of cases, respectively [12]. In this study, the drivers for the CSF microscopic examination sensitivity were (i) the number of samples per patient (sensitivity ranged from 37% to 87% when one to three CSF samples were analyzed, despite treatment initiation), (ii) the volume of CSF available (from 10 to 15 mL at best), and (iii) the examination of the CSF sediment. In a large European retrospective study involving 14 countries [13], 506 patients presenting with confirmed (a positive microscopic examination and/or a positive CSF culture on specific medium and/or a positive PCR) central nervous system tuberculosis were selected. Authors observed that CSF cytology yielded 320 ± 492 NC/mm3, with a predominance of lymphocytes (67 ± 26%), CSF protein level at 3.1 ± 4.2 g/L, and CSF glucose level/glycemia ratio of 0.28 ± 0.15. Culture sensitivity on Lowenstein medium was 72.6% and the sensitivity of the microscopic examination was 27.3%. This low performance of direct examination is probably due to the low inoculum of *M. tuberculosis* in CSF, the bacteria being located in cells of tissues, not in the fluid.

Several authors suggested using CSF adenosine deaminase (ADA) titration as a criterion to discriminate tuberculous meningitis from other bacterial meningitis types, but the performance of this test is debated. The authors of a meta-analysis reported sensitivity and specificity of ADA titration of 79 and 91% in the diagnosis of central nervous system tuberculosis, with positive and negative likelihood ratio of 6.85 and 0.29, respectively [14]. Another study [15] reported a lower sensitivity for ADA titration (55%). Nevertheless, the recent European study reported a positive ADA in routine practice in only 41/137 cases (29.9%) [13]. So far, this test is not recommended in recent guidelines [16].

PCR could be a better tool for diagnosing CNS *M. tuberculosis* infection. Unfortunately, there is no standardized PCR for CSF, so far, and performance of this test is linked to the experience of the microbiological laboratory and the used marketed PCR. The authors of a 2013 study of 235 South African patients presenting with *M. tuberculosis* meningitis [17] observed that the quantitative Xpert MTB/RIF PCR, versus culture and/or Amplicor PCR, was associated with a better

sensitivity than that of a clinical score or the CSF microscopic examination (Gram and auramine staining): 62% versus 30% and 12%, respectively ($P = 0.001$). Sensitivity was better when the CSF sample had previously been centrifuged (82% vs 47%), which required 3 mL of CSF (instead of 1 mL). South Africa being an endemic country for tuberculosis, PPV and NPV of the Xpert MTB/RIF test were 90 and 77%. A meta-analysis of eight studies was published in 2014 and revealed that the sensitivity and specificity of the Xpert MTB/RIF test in CSF, as compared with culture, were 81 and 98%, respectively [18]. The authors of the multicenter European study observed 57.3% sensitivity for *M. tuberculosis* PCR [15]. This sensitivity was measured using the analysis of heterogeneous PCR techniques: PCR-hybridization (Cobas®Amplicor, Grenzach-Wyhlen, Roche, Germany), RT-PCR (ProbeTec®, Becton Dickinson, Oxford, UK), GeneProof® (GeneProof, Brno, Czech Republic), and GeneXpert® (Cepheid, Sunnyvale, CA, USA),which makes impossible evaluating the sensitivity of each of these techniques. The European authors also highlighted the possibility of performing a blood IGRA test (QuantiFERON®-TB Gold In-Tube test) and reported good results: 37 positive results out of 41 tested (sensitivity of 90.2%).

9.7 Imaging

Brain MRI is the best tool for diagnosis of encephalitis, and CT scan should be used only when MRI is impossible [16].

There are no specific images for tuberculous encephalitis, except in case of brain abscess or granulomatous lesions. In the recent study [3], CT scan and MRI were normal on admission for 8 patients out of 17, meaning it is impossible to reject diagnosis of tuberculosis in case of normal images.

9.8 Treatment

9.8.1 Standard

Delays in initiating the antimicrobial treatment in encephalitis tuberculosis patients are associated with an increased mortality and a risk of neurological sequelae [19]. An empirical treatment is most frequently initiated because of the difficulty in establishing the final diagnosis (based on bacteriological or histological data) and of the poor sensitivity of rapid diagnostic tests [20]. Before confirmed diagnosis, clinical deterioration or rapid improvement should not lead to early discontinuation. One should keep in mind that specific antituberculous treatment may be associated with long onset of action, especially in patients presenting with severe brain damage. The empirical treatment should thus be administered, once decided, for the whole

scheduled duration, unless a final alternative diagnosis is established [21]. Some suggested administering intensive 6-month treatments [22]. Nevertheless, the standard recommended treatment is the usual combination of four molecules (rifampicin, isoniazid, pyrazinamide, and ethambutol) administered for 2 months, followed by a dual combination therapy for an overall treatment duration of 9–12 months [23–25]. Unexpected treatment discontinuation is an independent risk factor for mortality in patients presenting with central nervous system tuberculosis [26] that argues in favor of the standard long-term treatment.

Isoniazid is a rapidly bactericidal agent, with a good CSF diffusion [27]. After administration of the usual doses (3–5 mg/kg/day), the obtained CSF concentrations of isoniazid are 10–15 times the minimum inhibitory concentration of *M. tuberculosis* [28]. Several authors suggested increasing isoniazid dosage to more than 5 mg/kg/day, i.e., 10–20 mg/kg/day in children. However, its excellent CSF diffusion does not support this increase in case of susceptible *M. tuberculosis* strain. Isoniazid may thus be administered by rapid intravenous route, associated with pyridoxine supplementation (one dose at a time).

Rifampicin does not reach so important CSF levels: they are <30% of serum concentrations [27]. Nevertheless, mortality related to central nervous system tuberculosis resistant to rifampicin confirms this antibiotic as a key partner in the treatment [29]. Considering its lower central nervous system diffusion, rifampicin has been administered at a dosage of 20 mg/kg/day in children, with good tolerability. Similar doses are used for bone and joint infections, without any safety issue. There is no benefit on mortality when using higher doses of rifampicin (600 mg IV versus 450 mg per os) and moxifloxacin (800 mg versus 400 mg per os) in patients presenting with central nervous system tuberculosis, in addition to a standard treatment with isoniazid, pyrazinamide, and corticoids [30]. Considering the above data, the usual dosage of rifampicin is recommended (10 mg/kg/day).

Pyrazinamide has a good oral bioavailability and a good CSF distribution [31]. It has been used at a dosage of 40 mg/kg/day in children and 30 mg/kg in adults, without exceeding 1.5 g/day [22].

Ethambutol is usually suggested in fourth position [27], despite of its poor diffusion in CNS (especially in the absence of inflammation).

9.8.2 M. Tuberculosis *Resistant*

Fluoroquinolones are an alternative, especially when dealing with resistance or contraindication to one of the molecules included in the "usual" four-drug combination. However, they must be avoided in pregnant or breastfeeding women, as well as for long treatment durations in children [32]. Among fluoroquinolones, moxifloxacin is supposed to have the best activity [33–35]. For single resistance to isoniazid (high-level resistance), it is recommended to replace isoniazid with a fluoroquinolone, for 2 months, and then to continue with a three-drug combination with rifampicin,

pyrazinamide, and a fluoroquinolone for an overall treatment duration of 12 months. For low-level resistance to isoniazid, the agent should keep on being prescribed nonetheless. For single resistance to rifampicin, it is recommended to replace rifampicin with a fluoroquinolone, for 2 months, and then to continue with a three-drug combination with isoniazid, pyrazinamide, and a fluoroquinolone for a total duration of 18 months [23]. Linezolid has also been successfully used [36], but it is restricted to cases of multidrug-resistant strain when combined with second-line treatments.

9.8.3 Adjuvant Therapies

Corticoids may improve the outcome related to noninfectious disorders (brain edema, vasculitis). The addition of a corticoid therapy is based on the extrapolation of findings from studies on tuberculous meningitis that suggested that non-HIV-infected patients must receive corticoids with an antituberculosis treatment, regardless of disease severity [26, 37]. The usual recommended dosages of dexamethasone or prednisolone are 0.4 mg/kg/day for adults and 0.6 mg/kg/day for children. The corticoid therapy is usually administered for 4 weeks, followed by a progressive weaning off over 4 weeks. British guidelines recommend using dexamethasone 0.4 mg/kg/day when neurological signs are observed and 0.3 mg/kg/day in the absence of consciousness disorder or focal neurological signs [23].

In case of persistent cerebral edema despite the administration of corticoids or for immune reconstitution inflammatory syndrome (IRIS), some reported clinical case studies with the use of interferon gamma [38], infliximab (anti-TNF) [39], and thalidomide [40]. Acetyl salicylic acid could have an anti-inflammatory action on mycobacterial infections (inhibiting the expression of eicosanoids and pro-inflammatory TNF) [41]. The authors of two recent studies showed that acetyl salicylic acid reduced the incidence of hemiplegia, stroke, and death in patients presenting with tuberculous meningitis (especially with genotype *LTA4H*) [42, 43].

9.8.4 Surgery

In case of tuberculous encephalitis, hydrocephalus and brain abscesses are the main indications for urgent neurosurgery. It aims at reducing intracranial pressure and bacterial inoculum in case of brain abscesses [44]. Surgical drainage may also be a diagnostic tool (histology, culture, and *M. tuberculosis* antimicrobial susceptibility testing). External ventricular drainage should be urgently performed when life-threatening hydrocephalus is suspected.

9.9 Outcome, Prognosis

In the French study [3], they did not include patients infected with multidrug-resistant strains. Nevertheless, six (33%) patients died during hospitalization. Ten out of 12 (78.6%) had persisting neurological symptoms on discharge. Despite non-multiresistant MT strains, the case fatality rate among tuberculous encephalitis patients was high in this series, compared to other aetiologies. The case fatality rate in other aetiologies (including HSV) was 9% that was a significative difference.

Authors of a multicentric multinational study [45] propose a score for unfavorable outcome of tuberculous meningitis. Unfavorable outcome was reported in 33% of patients, strictly similar to the one observed in encephalitis, that is, quite a validation of both findings. They used the following items to provide a severity index, having a linear correlation with the outcome: altered consciousness, altered consciousness plus nausea, vomiting, diabetes mellitus, immunosuppression, neurological deficit, hydrocephalus, and vasculitis. This score is not validated in encephalitis, but it is probable it could be, and anyway it is a basis, so far, for an evaluation of prognosis.

Despite management in a high-income country, tuberculous encephalitis presents with a poor outcome, even in case of sensitive strains.

9.10 Conclusion

Tuberculous encephalitis is still a burden in high-income countries. It is a frequent aetiology, difficult to assess, with a poor income despite an adequate treatment.

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