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## Epidemio-clinical aspects and neuro-meningeal tuberculosis prognosis in Batna

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### Abstract

Neuromeningeal tuberculosis is rare, affecting around 1-2% of all tuberculosis cases and 5% of extra pulmonary tuberculosis cases. Our aim is to describe the epidemio-clinical, prognostic and evolutionary aspects of neuromeningeal tuberculosis.

**Materials and methods:** To determine the spectrum of etiological agents of HIV-negative encephalitis and meningoencephalitis in Batna, we conducted a prospective study using an expanded testing approach. Patients were recruited from three departments (intensive care unit, infectious diseases department, pediatrics) during the period from April 1, 2012, to August 31, 2015. Data were collected according to the FLIPS case definition with a standardized form. We sought to identify etiological pathogens following a standardized procedure and to describe the epidemiological, clinical and biological features and outcomes associated with different causes.

**Results:** A total of 141 patients with infectious encephalitis and meningoencephalitis were included in the study. Bacterial etiology was determined in 65/141 (46.1%) of whom 30 cases (21.3%) were of tuberculous origin; 21 confirmed and/or probable cases 9 possible cases with high clinical, epidemiological and radiological probability. The median age was 30.5 (0-83), predominantly female 12/18, 23.3% comorbidity with a frequency of motor deficits (86.7%) and psychiatric disorders (26.8%), respiratory involvement was present in 60% of cases, pleocytosis was present in 22/25 (73.4%). hyperalbuminorachy in 66.7%, and hypoglycorachia in (46.7%). Anti-tuberculosis treatment was instituted in 90% of cases, 17.6% were initially admitted to an intensive care unit, and the median length of hospital stay was 38.5 (1-146). death was identified in 46.6%, with 10% having sequelae.

**Conclusion:** In our study, in addition to viruses, bacteria (especially intracellular) can be responsible for encephalitis and meningoencephalitis, in varying proportions. The most frequent and leading form of bacterial meningoencephalitis in adults is tuberculosis, the prognosis of which depends on early treatment.

**Keywords:** Tuberculosis; Encephalitis; Meningoencephalitis; Culture; PCR

### 1. Introduction

Neuromeningeal tuberculosis is rare, accounting for around 1-2% of all tuberculosis cases and 5% of extra pulmonary tuberculosis cases [1-4].

Despite anti-tuberculosis treatment, the prognosis remains poor, with almost half of cases progressing to death or severe sequelae [5].

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In Algeria, according to Ali Halassa, PHNI, March 24, 2011, out of 21838 reported cases of TBC, 11770 were of extra-pulmonary localization (54%), including 1% of neuromeningeal localization. According to the WHO, the rate of resistance to anti-tuberculosis drugs in Algeria was 14/809 (1.7%) [6].

Pulmonary infection with *M. tuberculosis* is complicated by bacteremia, which leads to the formation of Rich foci in meningeal and subcortical areas. These foci rupture into the subarachnoid space, producing a thick inflammatory exudate with a gelatinous consistency, preferentially located in the sylvian fissures, basal cisterns, brain stem and cerebellum. The presence of this exudate can have several consequences [7] including inflammation of small and medium-sized vessels, obstruction of CSF circulation, difficulty in CSF resorption [8] and spinal cord involvement in less than 10% of cases.

Encephalitis is generally contiguous with meningeal exudate, explaining the preferential involvement of the brain stem. Its preferential location at the base of the skull (rhombencephalitis) explains the frequency of involvement of cranial nerves and encephalic arteries. Diagnosis is hampered by the lack of specificity of clinical and paraclinical features, and the low sensitivity of diagnostic tests such as CSF culture or PCR. The presence of a high-risk background and a subacute course of 2 to 3 weeks are suggestive of the disease. A history of tuberculosis is found in only 10% of cases. The notion of a tuberculosis contact sought on questioning is present in only 20 to 25% of cases [6]. Symptoms are usually chronic, evolving over several weeks or months. Associated pulmonary involvement is common (30-75%), with radiological abnormalities in 25-75% of cases, depending on the series [9-14]. Signs of tuberculosis in another site are suggestive of the disease. The fundus is highly suggestive when it reveals Bouchut's tubercles (less than 10% of cases).

Hyponatremia is classic but non-specific. CSF is typically clear or opalescent. The appearance of a cobweb-like film on the surface of the CSF, when stagnant at room temperature or in the refrigerator, is fairly characteristic, but not pathognomonic. Elements rarely exceed 300/ml. The formula is variable, predominantly lymphocytic, but a majority of polynuclear cells may be present initially, becoming increasingly rare as the disease progresses [15].

Hypoglycorachy correlates with a more advanced stage of the disease, and proteinorachy between 1.5 and 2 g/L [16]. A very high proteinorachy suggests a spinal block in the context of peri-medullary arachnoiditis.

Direct examination for mycobacteria is positive in only 15-20% of cases. Analysis of large quantities of CSF, possibly obtained by repeated punctures, even within 48 hours of initiation of treatment, increases positivity rates [17]. Cultures only become positive after 3 or 4 weeks in solid media, and 1 or 2 weeks in liquid media. The existence of extra-neurological localizations increases the chances of obtaining a positive microbiological or anatomopathological sample in 75% of cases [1].

PCR has a specificity of 98% and a sensitivity of 56% in CSF [17, 18], up to 1 month after the start of treatment [17, 19].

The (QuantiFERON-TB), in neuromeningeal forms, has a 50% false-negative rate [20].

The most suggestive abnormalities are more or less precocious hydrocephalus (up to 70% of cases), hyperdense meningeal spaces (basilar meningitis) (45%), ischemic lesions (25%) and rarely associated tuberculomas, but none of these abnormalities is strictly specific [16].

Symptoms may worsen under anti-tuberculosis treatment. Corticosteroid therapy aims to attenuate inflammatory phenomena and reduce the side-effects of anti-tuberculosis drugs [21].

Mortality in neuromeningeal tuberculosis remains in the order of 20 to 40%, while sequelae are present in 20 to 50% of cases, depending on the series [1, 8, 15].

Our aim is to describe the epidemiological, clinical, prognostic, and evolutionary aspects of neuromeningeal tuberculosis.

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## 2. Material and methods

During the period from April 1, 2012 to August 31, 2015 a prospective, longitudinal and exhaustive study had focused on patients aged over 28 days with symptoms suggestive of encephalitis meeting the inclusion and exclusion criteria established by the FLIPS[22], from three medical departments (intensive care, infectious diseases and pediatrics) with

a study of epidemiological, clinical, biological, radiological and etiological parameters, reported on a standardized form that was completed upon patient admission. HIV-positive patients were excluded.

Samples were taken on admission, in accordance with standard procedures for the management of suspected cases of encephalitis. Lumbar puncture (LP) was performed in 131 (92.9%) patients. This LP was missing in 10 patients (7.1%), 4 of whom had pupillary edema, 2 had spondylodiscitis and 4 had neuromalaria, or the etiology was sought in other samples, notably serum, or in other secondary locations.

Due to lack of volume, glycorrachy was performed on only 129 CSFs (98.47%) and albuminorachy on only 124 CSFs (94.65%). In addition, for further microbiological investigation, samples were taken and immediately frozen at -80°C for subsequent analysis (blood on EDTA tube (5 ml) or dry tube (5 to 10 ml), throat swab, CSF (1 tube of 15 drops each). These samples were supplemented by blood on EDTA tube (5ml) or dry tube (5ml) taken at the patient's discharge.

PCR/RT-PCR, viral culture and serologies were performed secondarily at the Agents Infectious Institute (IAI) at Lyon University Hospital. Additional molecular analyses were carried out in accordance with IAI microbiology laboratory standards. Samples were extracted on Nuclisens Easymag (Bio Mérieux).

In line with the recommendations of the FLIPS [22], the proposed investigation is divided into three successive levels, from the most urgent and frequent encephalitis infections, to the rarest and most difficult to interpret cases, and the classification of cases was created to specify the level of evidence between the microbiological result obtained from the analyzed samples and the etiological link of the encephalitis observe.

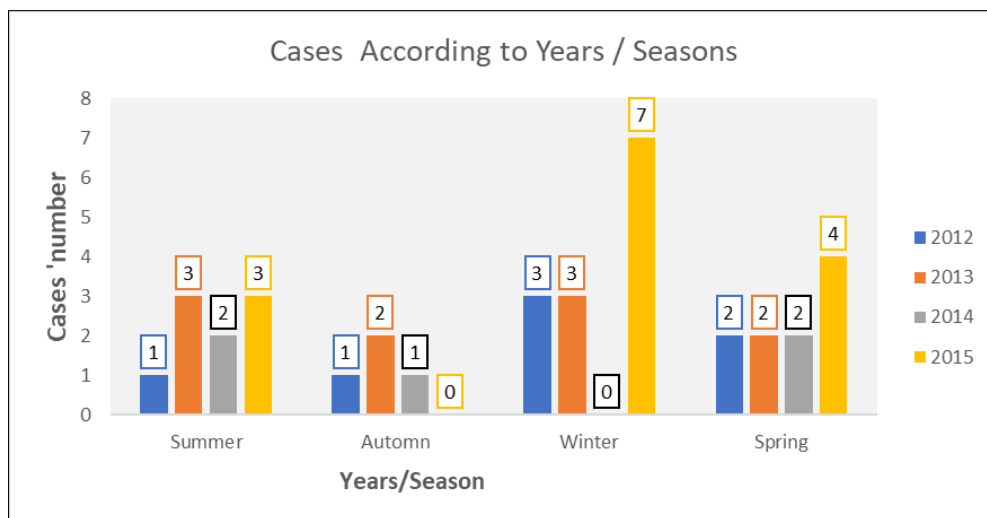
Depending on the result, the etiology identified for each case is classified as confirmed, probable, possible or unknown.

We were able to test 2671 PCR samples, 404 direct tests and bacterial cultures, 219 viral cultures and 380 serologies. The number of pathogens tested for the patients included in this study ranged from 1 to 31 pathogens. For 13 patients, only one test was carried out, as it was immediately positive.

### 3. Results

A total of 141 patients with infectious encephalitis and meningoencephalitis were included in the study.

The mean number of agents investigated was 15.01 for patients with a diagnosis and 20.17 for patients without a diagnosis.



**Figure 1** Cases according to years /Seasons

Bacterial etiology was determined in 65/141 cases, i.e. 46.1%, of which 30 cases, i.e. 21.3% were of tuberculous origin; 21 confirmed and/or probable with 8 co-infections (LCS: EBV. Serum: 3 CMV ,1 HSV2. PP: 4 Coronavirus). 9 possible cases with high clinical, epidemiological and radiological probability, with 3 co-infections (LCS: CMV, BK virus, PP: Coronavirus). Median age was 30.5 (0-83), predominantly female 12/18, 23.3% comorbidity, 6.7% history of

psychiatric disorders. Nearly 50% of patients were recruited in 2015, most of them in winter, 56.7% had signs of tuberculosis impregnation. A high frequency of motor deficits (86.7%) and psychiatric disorders (26.8%), respiratory involvement was present in 60% of cases, pleocytosis was present in 22/25 (73.4%), hyperalbuminorachy in 66.7%, and hypoglycorachy in (46.7%). TST was positive in 23.4% of cases, hyponatremia in 21 (70%). Neuroimaging was abnormal in 90% of cases; 17.6% were initially admitted to an intensive care unit, the median length of hospital stay was 38.5 (1-146). death was identified in 46.6% with 10% of sequelae.

**Table 1** Patient distribution according to clinical table

Clinic	Effective (n: 30)	%
Progressive start	27	90%
Tuberculosis impregnation signs	17	56.7%
Meningeal stiffness	19	63.3%
Consciousness disorders	19	63.3%
Cranial pairs damage	08	26.7%
Behavioral disorders	22	73.3%
Seizures	15	50%
Psychiatric disorders	08	26.7%

**Table 2** Patient distribution according to biology

Biology	Effective (n : 25)	(%)
Pleiocytosis	22	73.4%
Lymphocytic	14	46.7%
Polynuclears	05	16.7%
Panachee	06	20%
Natraemia	/	/
IDR	/	/

**Table 3** Patient distribution by radiological picture

Radiological lesions	N Effective (n : 27)	(%)
Hydrocephalus	14	46.7%
Tuberculomas	12	40%
Edema	11	36.7%
Arachnoiditis	09	30%
Cerebellar damage	04	13.3%
Ischemic lesions	02	6.7%
Rhombencephalitis	01	3.3%

#### 4. Discussion

In Batna, a wide range of pathogens cause encephalitis and meningoencephalitis. Of the 141 patients collected, and using a global approach and state-of-the-art diagnostic methods, the etiology was identified in 65 cases (46.1%) vs. 14.6% in France in 2007[22], 43.8% in England 2005-2006[23], 8.9% in California 98-2005[24], 0.2% in PMSI France 2000-200[25].2, 8.1% in Thailand 2003-2005 [26].

Of these 65 cases, 30 or 21.3% were of tuberculosis origin, compared with 1% in California 1998-2005[24], 8% in France 2007[22], and 5% in England 2005-2006[23].

In our country, given the endemicity of tuberculosis, tuberculous meningoencephalitis is particularly oriented by the existence of clinico-epidemiological or radiological signs in favor of basilar meningitis or the demonstration of hydrocephalus, all the more so when the CSF is lymphocytic, hyperproteinorachic and hypoglycorachic [11]. The frequency of cases detected in our 30-case study bears witness to this: 21 confirmed and/or probable cases with 8 co-infections (CSF: EBV. Serum: 3 CMV, 1 HSV2. PP: 4 Coronavirus). 9 possible cases with high clinical, epidemiological and radiological probability, with 3 co-infections (CSF: CMV, BK virus, PP: Coronavirus). There were 17 confirmed cases (56.7%); 2 by brain biopsy, the rest by CSF culture. Probable cases numbered 4 (culture of secondary localizations). Possible cases: cases of tuberculoma, 3 cases of spondylodiscitis, tuberculoma-arachnoiditis, only reinforced the diagnosis of tuberculosis. A high proportion of adult cases were observed, with a median age of 30.5 (0-83) vs. 61 (17-79) in France [22]; predominantly female, with a sex ratio of 0.66. These results are more or less similar to those found in Morocco in the neurosurgery department of the IBN Sina HUC in Rabat [11], where the population had an average age of 26 years (13-65) with a female predominance. In contrast, a study carried out in Nouakchott described a predominance of males, with a sex ratio of 1.4 (Reference).

The mode of onset was progressive in 90% of cases, in line with the literature and far exceeding the results found in Meknes, where progressive onset was observed in only 28.6% of cases [27].

Through our study, signs of tuberculosis impregnation were present in 56.7% of cases, meningeal stiffness was manifest in 63.3% of cases, these results being close to those of a Tunisian study with 54.1% of cases [28] ; while involvement of the cranial pairs and motor and sensory deficits were noted in only 26.7% and 27.8% of cases respectively, in line with what has been reported in Tunisia[28].

Consciousness disorders were found in 63.3% of cases, in contrast to those observed in a Tunisian study [27], where they were found in only 31.3% of cases. The 50% of cases with convulsions are in line with the results of a Tunisian study, which showed convulsions in 78.3% of cases [28].

In general, signs of neurological focalization appear to be more constant with *Mycobacterium tuberculosis*, their frequency ranging from 22 to 83% of cases [29-31]. In our study, focal neurological disorders were present in 86.7% of cases vs. 62% in France [22], while behavioral disorders were evident in 73.3% of cases, in line with those found in Morocco's Hassen II HUC [32]. Myelitis was found in only 10% of cases, but psychiatric disorders were objective in 26.7% (12.4 IC 95% (1.4-105.8) p=0.006).

Pleiocytosis was found in 73.4% of cases; lymphocytic in 46.7%, polynuclear in 16.7% and variegated in 20%.

Clear CSF was predominant, concordant with the results of most studies, with 47.1% of cases in Tunisia [28], 51.2% in Rabta Hospital, Tunisia [33].

Hypoglycorachy was noted in 46.7% of cases, and Hyperproteinorachy in 66.7% of cases; our results are inferior to those found in the Tunisian series where hypoglycorachy and Hyperproteinorachy were observed respectively in 62.1% and 70.1% of cases in the first series [33, 34] and 85.7% and 70% in the second series [27].

Through our study, a high proportion of abnormal pathological neuroimaging (90%); this is in line with the literature [34], certain images of which point to tuberculosis (notably hydrocephalus 46.7%, tuberculomas 40%, and arachnoiditis 30%). However, it is dependent on the availability of equipment, its quality, and the expertise of the image reader [35] and is still insufficiently available in Algeria. The association arachnoiditis-tuberculoma was noted in (23.4%). A more obvious result than what was detected in Tunisia: 14.9% for hydrocephalus and 21.4% for arachnoiditis, with the exception of tuberculomas where their frequency was 53.7% of cases [33].

According to Amène Aïssa<sup>1</sup> et al Hydrocephalus accounts for 65% of cases of tuberculosis secondary to arachnoiditis, which accounts for 50%. Tuberculoma, arachnoiditis and vasculitis are all highly specific for the diagnosis of tuberculosis [36]

The average length of hospital stay was 38.5 days (1-146).

In the light of our study, we deplore 46.7% of deaths, far surpassing the Tunisian study with 9.52% and that of Dollo et al. [37] who found 31%.

This high death rate, compared with other studies in France and Thailand [38-41], could be explained by a delay in diagnosis.

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## 5. Conclusion

In our study, in addition to viruses, bacteria (mainly intracellular) can be responsible for encephalitis and meningoencephalitis, in varying proportions. The most frequent and leading cause of bacterial meningoencephalitis in adults is tuberculosis, whose prognosis depends on early treatment. The diagnosis must be evoked at the slightest doubt and lead to a lumbar puncture. Analysis of the CSF remains the main diagnostic step, complemented by less specific but increasingly effective brain imaging.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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