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RESEARCH ARTICLE

Cerebro-Meningeal Tuberculosis in HIV-Negative Adults

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Abstract

Background: Tuberculosis remains a public health problem worldwide. Neurological localization is the most severe manifestation of extra-pulmonary tuberculosis characterized by a high mortality rate and a high rate of sequelae among survivors; its diagnosis is hampered by the absence of rapid and accurate tools, therefore it is often evoked and treated on presumption arguments. The aim of this study is to assess the epidemiological, clinical, diagnostic, treatment, and outcome features in patients with cerebro-meningeal tuberculosis in Setif-Algeria.

Methods: We retrospectively studied the patient files followed for cerebro-meningeal tuberculosis at the infectious diseases department of the teaching hospital of Setif-Algeria from January 2005 to December 2016. Patients entered corresponded to the consensus cases definitions established in Cape Town-South Africa in 2010.

Results: The included patients were 45 women and 26 men of nearly 41.7 years old (16-86). A history of tuberculosis had affected 6 patients and the disease was associated to extra-neurological tuberculosis in 37 patients. According to British Medical Research Council Staging of tuberculous meningitis, 23 were in stage I, 17 were in stage II, and 31 were in stage III. Neurological deficits are seen in 35 cases, they were numerous and various in some individuals. Cerebral imaging was pathological in 37 cases, multiple lesions were found: tuberculomas (21 cases), hydrocéphalus (10 cases), vascular lesions (7 cases), basal meningeal enhancement (21 cases)...etc. Magnetic resonance imaging was more contributive than cerebral tomodensitometry. 5 patients died and 13 had neurological sequelae with varying degree.

The study showed that cerebral imaging was more pathologic in women ($p = 0.01$), and in people less than 65 years old ($p = 0.04$). The rate of death is more significant in elderly subjects ($p = 0.001$). Tuberculoma, hydrocephalus, and low cerebrospinal fluid glucose levels increase significantly when the diagnosis is delayed.

Conclusion: Prompt diagnosis and early treatment are crucial to the successful management of tuberculous meningitis. Culture of *Mycobacterium tuberculosis* is too slow and insensitive to aid clinicians to make diagnosis. Therapeutic decision must be, to date, made on presumptive arguments and independently of the confirmation means.

Keywords

Tuberculosis, Cerebro-meningeal, Diagnosis, Mortality, Treatment

Introduction

Tuberculosis remains one of the world's biggest threats to public health. The increasing prevalence of tuberculosis in both immunocompetent and immunocompromised individuals in recent years makes this disease a topic of universal concern. The World Health Organization estimated the new tuberculosis cases at 10.4 million and the number of death at 1.4 million people in 2015 [1].

Central nervous system involvement occurs in 1-2% of all tuberculosis patients and 6% of extra-pulmonary disease [2,3]. The bacilli reach the central nervous system in most cases by hematogeneous spread usually from a pulmonary focus. Central nervous system infection causes a granulomatous inflammatory reaction (Rich's foci) that involves the meninges and/or brain parenchyma. Inflammatory exudate can obstruct the flow of cerebrospinal fluid (CSF) and causes hydrocephalus. Adhesions can compromise cranial nerves and an obliterative vasculitis of both large and small vessels which result in infarction and stroke syndromes. Granulomas can coalesce to form tuberculomas, causing diverse

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clinical problems depending on their size and location [4,5].

A study of immunological parameters showed a relation between the development of tuberculous meningitis in children and significantly lower count of CD4 T-lymphocytes when compared with children who had pulmonary complex only [2]. Another study done in Vietnam has speculated on the relationship between bacterial and host genotype as being responsible for genesis of extrapulmonary versus pulmonary disease [6].

A high rate of tuberculous meningitis in adults is an evidence of a not controlled germ reservoir in the community. Tuberculous meningitis is highly devastating; it carries a high mortality and a distressing level of neurological morbidity. It is also difficult to diagnose and treat; clinical features are polymorph and non-specific; conventional bacteriology and newer diagnostic techniques such as those that use polymerase chain reaction (PCR) are insensitive. Currently clinicians depend on the discriminative clinical and laboratory features of the disease for successful diagnosis and treatment. Many studies have tried to identify simple clinical and CSF findings predictive of an early diagnosis of tuberculous meningitis by using multivariate logistic regression in order to develop a diagnostic rule. All of them have had varying degrees of sensitivity and specificity and have demonstrated that applying this diagnostic rule can help in the early diagnosis of tuberculous meningitis [7].

The aim of our study is to describe and analyze the epidemiological, clinical, diagnostic, treatment, and outcome features of patients with cerebro-meningeal tuberculosis in a teaching hospital in Setif-Algeria.

Material and Methods

A retrospective study was carried out on the files of patients hospitalized between January 2005 and December 2016 for cerebro-meningeal tuberculosis. 71 patients who entered the study corresponded to the consensus cases definitions established in Cape Town-South Africa in 2010 [8]. According to this consensus, we found “Definite tuberculous meningitis” in 14 cases, “Probable tuberculous meningitis” in 35 cases and “Possible tuberculous meningitis” in 22 cases. HIV test was negative in all patients.

A statistical study was done by the Epi-Info software version 3.5.4. We started with a descriptive analysis for all variables studied: epidemiological (age, sex, antecedents, underlying pathology), clinical (delay of diagnosis, general signs, neurological signs, associated extra neurological tuberculosis), diagnostic procedures (brain imaging, CSF results, isolation of *Mycobacterium tuberculosis…),* and prognosis. A bivariate analysis was done using the chi-square test (χ^2) or Fisher test (when the number of patients is reduced) with a 5% statistical significance level and calculating measures of epidemiological associations (Odds-ratio: OR with 95% confidence interval (CI)).

Results

71 patients (females 45 and males 26) were included in this study with an average age of 41.7-years-old (16-86). A history of tuberculosis was found in 6 cases and an underlying pathology in 12 cases including two diabetics, one pregnant woman and two women who had recently given birth.

The start mode was sub-acute with an average diagnosis time of 38.4 days (8-400 days) and a median of 20 days. Evaluation of clinical severity according to British Medical Research Council Staging of tuberculous meningitis [9] found, 23 (32.4%) stage I, 17 (23.9%) stage II and 31 (43.7%) stage III. The clinical picture was rich, made of general, neurological, and extra neurological signs (Table 1). Neurological deficit noted in 35 cases were numerous and various in some individuals: 1 sign: 15 cases, 2 signs: 12 cases, 3 signs: 6 cases, 4 signs: 1 case and 5 signs: 1 case.

Associated extra neurological tuberculosis was found in 37 patients, 8 of them had more than 2 localizations. Pulmonary involvement was found 29 times including 14 miliary aspects at the chest X-ray.

All patients were investigated with cerebral tomodensitometry and/or Magnetic Resonance Imaging (MRI). Cerebral imaging was pathological in 37 cases; the radiological aspects were numerous and varied (tuberculomas, hydro-

Table 1: Clinical signs found in patients.

Clinical signs	Number (%)
Tuberculous impregnation general signs	42 (59.2)
Fever > 38 ºC	61 (85.9)
Glasgow score < 10	08 (11.3)
Behavior abnormality	02 (02.9)
Neurological deficits:	35 (49.3)
Convulsions	19
Hemiparesis or Hemiplegia	07
Cerebellar syndrome	03
Paraplegia	06
Oculomotor palsy	14
Blindness	02
Aphasia	01
Facial palsy	03
Trigeminal neuralgia	01
Urinary retention	08
Associated extra neurological tuberculosis:	37 (52.1)
Pulmonary miliary	14
Pneumopathy	15
Spondylodiscitis	06
Adenopathy	05
Ascites	01
Pleurisy	04
Testicular nodule	01
Splenic nodule	02
Cutaneous tuberculosis	01
Medullary tuberculoma	03

cephalus, vascular lesions ... etc); MRI was more contributive than tomodensitometry in 21 cases out of 34 who benefited from both explorations (Table 2).

The number of tuberculomas varied from the single lesion to the miliary form found 10 times; they were in supratentorial region (5 cases), in infratentorial region (2 cases), and in the two floors of the brain (14 cases).

The vascular pathology was in most cases feminine; only one man had an ischemic injury. Arterial damage affected different areas: right posterior cerebral (1 case), right peri-sylvian (2 cases), and the left peduncle (1 case). Venous thrombosis was varied and sometimes multiple in the same patient: sagittal sinus (2 cases), lateral sinus (2 cases) and transverse sinus (1 case) [10].

A total of 66 patients had a lumbar puncture; the white cell count was elevated in 64 patients with lymphocyte predominance. The average number of cells was 179/mm^3 (11-744 cells/mm^3), only 2 patients had a greater than 500 cells/mm^3. Protein levels were elevated in 45 patients (70.3%), among these ones 9 of them had above 2 g/L. The glucose content was low in 44 patients (68.6%).

Mycobacterium tuberculosis was isolated in the CSF in 14 patients and at another location in 7 patients. The anatomopathological study participated in the diagnosis of an extra neurological localization in 7 patients. Drug sensitivity tests were not performed in our series. All patients have been treated with rifampicin, isoniazid, ethambutol, and pyrazinamide in the first 2 months of the intensive phase of treatment followed by rifampicin and isoniazid in the continuation phase of 7- 10 months. This continuation phase has been prolonged more than year (18 months) when tuberculomas persist. Pyrazinamide and isoniazid were discontinued in 10 patients due to hepatotoxicity, in these cases ofloxacin was included and sometimes amikacin.

Corticosteroids were used in 47 patients. Dexamethasone was generally used at an initial dose of 0.4 mg/kg/24 hours according to the British Infection Society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system [11] with a gradual reduction over 8-12 weeks.

The average hospital stay lasted 31.5 days (3-100 days). 52 patients had full recovery and 13 patients had saquelae: 2 blindness, 1 epilepsy, 5 motor deficits, 6 oculomotor paralysis, and 1 psychiatric disorders. One patient presented a relapse after 2 months of completed treatment and 5 patients died; all of them were at the

Table 2: Radiological aspects of brain imaging.

Image type	Number (%)
Imaging without abnormality	34 (47.9)
Basal meningeal enhancement	21(29.6)
Tuberculomas (nodular enhancing lesion with a central hypodense region):	21 (29.6)
1 lesion	05
2 lesions	01
3 lesions	02
4 lesions	01
5 lesions	02
Multiple and diffuse lesions	10
Ischemic vascular lesions	04 (5.6)
Cerebral venous thrombosis	03 (4.2)
Hydrocephalus	10 (14.1)
Tuberculous abscess (characterized by cavity formation with central pus)	02 (02.9)
Brain edema	05 (7.04)

Table 3: Variables with significant variation by sex, age, and diagnosis delay.

		Number (%)	OR [CI 95%]	p-value (X^2)
Significant variations by gender				
Oculomotor palsy	Women	12 (28.9)	10.16 [1.2-82.9]	0.008 (6.52)
	Men	1 (3.8)		
Pathological brain imaging	Women	28 (62.2)	3.11 [1.13-8.52]	0.01 (5.03)
	Men	9 (34.6)		
Tuberculomas	Women	18 (40.0)	5.11 [1.3-19.6]	0.009 (6.40)
	Men	3 (11.5)		
Significant variations by age				
Glasgow score < 10	Age < 65 years	3 (5.0)	10.7 [1.9-57.8]	0.009 (10.1)
	Age ≥ 65 years	5 (45.5)		
Mortality	Age < 65 years	1 (1.7)	0.03 [0.003-0.3]	0.001 (15.2)
	Age ≥ 65 years	4 (33.3)		
Pathological brain imaging	Age < 65 years	34 (57.6)	4.08 [1.001-16.62]	0.04 (4.2)
	Age ≥ 65 years	3 (25)		
Significant variations by delay diagnosis				
Tuberculomas	≤ 30 days	11 (23.9)	0.3 [0.1-0.9]	0.03 (4.4)
	> 30 days	10 (50.0)		
Hydrocéphalus	≤ 30 days	3 (6.5)	0.13 [0.03-0.57]	0.006 (8.8)
	> 30 days	7 (35.0)		
Low glucose levels in CSF	≤ 30 days	26 (61.5)	0.2 [0.04-0.99]	0.03 (4.4)
	> 30 days	18 (88.9)		

stage III of clinical severity.

In univariate analysis, we checked the influence of sex, age, and diagnosis delay on all variables studied. We noted that cerebral imaging was more pathologic in women, and in adults less than 65-years-old. The rate of death is more significant in elderly subjects. Tuberculoma, hydrocephalus and low glucose level in CSF increase when the diagnosis was delayed (Table 3).

Discussion

As several previously published series, this one confirms the serious nature of the disease. Moreover, several results characterize this study. The female predominance found is not common; so few studies have reported a discreet female predominance and others have found the opposite [7,12,13]. However, it has been clearly established that women develop more extra-pulmonary forms of tuberculosis than men [14].

A history of tuberculosis found in 8.5% is usual and has been reported at similar or even higher rates [12,15]. Associated extra meningeal tuberculosis is very helpful on clinical assessment; the presence of active pulmonary tuberculosis on chest X-ray ranges from 30 to 50%, but these findings lack specificity in areas with a high prevalence of pulmonary tuberculosis. However, miliary tuberculosis strongly suggests multiorgan involvement; meningeal involvement in pulmonary miliary is associated in 1 out of 5 cases. Medullary involvement (tuberculoma) observed in 2.8% of cases was about 10% in other series [16-18].

Clinically, there is a history of vague ill health lasting weeks prior to the development of meningeal irritation. These non-specific symptoms include malaise, anorexia, tiredness, fever, myalgias, and headache. Adults with tuberculous meningitis can often present with the classic meningitis symptoms of fever, headache and stiff neck along with focal neurological deficits, behavioral changes, and alterations in consciousness. Meningitis is the most common manifestation of cebromeningeal tuberculosis. Most of the clinical forms described in the literature (Tubercular Meningitis, Space occupying lesions: tuberculomas and tubercular abscess, Tubercular encephalopathy, Tubercular vasculopathy) have been observed in this study [5].

The severity of tuberculous meningitis classified into three grades according to the patient's Glasgow coma score and the presence or absence of focal neurological signs was shown to be strongly predictive of death, all death in this work were at stage III [18-24]. However, 49.3% of patients at the stage III is a high rate compared to other studies [20,25,26] and could be explained by delayed diagnosis.

Neurological deficits are usually due to the presence of tuberculomas or abscess, hydrocephalus and vascular involvement [27], the severity of these complications may be dependent on the intracerebral inflammatory response and strongly predicts outcome [28].

Cranial nerve palsies occur in 8-50% of patients and may be the presenting manifestation of tuberculous meningitis [21,29]. Blindness is the most serious of cranial nerve involvement; as regards to our patients, blindness was secondary to an optochiasmatic tuberculoma in one case and probably to the optochiasmatic arachnoiditis in the second case. The importance of oculomotor palsy in women ($p = 0.008$) and trijumal neuralgia have not been mentioned in the review of the literature that we have done.

MRI was more sensitive than tomodensitometry (61.8%) to identify inflammatory lesions such as granulomas, angeitis or arachnoiditis which confirms the value of MRI in this situation [30,31]; we specify that vascular lesions and some cases of tuberculoma have not been identified by the tomodensitometry. The significantly higher incidence of tuberculomas in women characterizes our study.

Cellularity of CSF often corresponded to the typical form with a leucocytosis under 500 cells/mm^3 mostly lymphocytes; atypical CSF findings are well described, particularly in immune-suppressed patients, and the CSF can be acellular or contain a predominance of neutrophils [18,32]. Increase protein level is observed in 90 à 100%; it is a factor of bad prognosis according to several series [22-24,32-34]. Low glucose content observed in 30-95% was 68.6%. [10,34,35] but the association between low glucose levels in CSF and delayed diagnosis is not common and needs to be clarified by other studies.

The definitive diagnosis of tuberculous meningitis is made by isolation of *Mycobacterium tuberculosis* from the CSF, by direct staining, or by culture. However, Ziehl-Neelsen smear sensitivity varies between 10% and 60% and culture positivity rates are between 25% and 75% [36,37]. Although the wide use of nested PCR assay in clinical practice is expected, regrettably, it has rarely been performed for tuberculous meningitis diagnosis. A recent systematic review and metaanalysis calculated that the sensitivity and specificity of commercial nucleic-acid-amplification assays for the diagnosis of tuberculous meningitis was 56% (95% CI 46-66) and 98% (97-99) respectively [38,39]. In view of this low sensitivity, the negativity of PCR should not be used to exclude the diagnosis of cerebro-meningeal tuberculosis.

The use of the antibody levels to detect antigens of *Mycobacterium tuberculosis* in the diagnosis has not been fruitful because of their poor specificities [40,41]; however a systematic review and meta-analysis done in 2017 have shown that adenosine desaminase test had a relatively high accuracy for the diagnosis of tuberculous meningitis [42].

The prompt diagnosis and treatment of tuberculous

meningitis saves lives. As our results, delays in diagnosis and treatment are regarded as major contributing factors in the high mortality reported in many recent series [21,24,33,43]. The mortality rate of 7% is significantly lower than those of endemic area and some developed countries as the United States [33,44] but it has been reported by some authors [23]. Proportion of patients with various neurological sequelae in our study is also lower than other studies [45].

Standard anti-tuberculous drugs were used in all patients according to national guidelines, but treatment duration of 6 months wasn't applied, it varied according the severity of the disease and evolution of tuberculoma. The optimum duration of treatment of tuberculous meningitis is unknown; however, most international recommendations recommend a duration of 9 to 12 months [46,47].

A high proportion of patients were treated with adjuvant corticosteroide; this is a well-established component of tuberculous meningitis treatment and has been shown to significantly reduce mortality rates [48,49].

Conclusion

Tuberculous meningitis, the most devastating form of tuberculosis, is associated with significant mortality and morbidity. Crucial to the successful management of tuberculous meningitis are prompt diagnosis and commencement of antituberculosis chemotherapy. The diagnosis of tuberculous meningitis relies on isolation of *Mycobacterium tuberculosis* from the CSF which is insensitive to aid clinical decision-making. Accordingly the decision to treat patient for tuberculous meningitis must be empirical, irrespective of the diagnostic facilities available to clinicians. More research is needed to improve clinical management and outcome of tuberculous meningitis.

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