ACTA SCIENTIFIC MICROBIOLOGY (ISSN: 2581-3226)

Volume 2 Issue 10 October 2019

Research Article

Clinical Presentations and Factors Associated with in-Hospital Mortality of Patients Diagnosed with Subacute and Chronic Infectious Meningitis in A Mexican Hospital

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Received: August 26, 2019; **Published:** September 05, 2019

DOI: 10.31080/ASMI.2019.02.0364

Abstract

Background: Subacute/chronic meningitis are well-characterized clinical entities whose differential diagnosis is broad and challenging to address, resulting in a third of cases without an etiological diagnosis. In the world literature and especially in our country few studies describe the clinical patterns of presentation of the most common forms of subacute/chronic infectious meningitis, as well as what is the relationship of these patterns to in-hospital mortality. Cases of chronic meningitis in our environment may be over diagnosed as tuberculous meningitis because of its high regional frequency. Thus, we seek to establish the frequency of diagnostic confirmation in our region as well as identify risk factors link to in-hospital mortality.

Methods: We studied clinical records of patients with a diagnosis of chronic and subacute meningitis at discharge in five years. Clinical and auxiliary test data were analyzed to find their association with in-hospital mortality.

Results: We found that the most frequent sign in this population was acute cognitive impairment (75.5%), followed by a headache. The majority of the cases was associated with meningeal tuberculosis. We found an association between immunosuppression, diminished level of arousal, prolonged time of disease progression, CSF acute inflammatory pattern, and hydrocephalus in the hospital mortality.

Keywords: Subacute and Chronic Meningitis; Tuberculous Meningitis; Cerebrospinal Fluid; Hydrocephalus

Introduction

Subacute and chronic infectious meningitis are well defined clinical entities although scarcely reported in medical literature [1]. While chronic meningitis is defined as a leptomeningeal inflammation with persistent neurological symptoms with cerebrospinal fluid (CSF) changes which include protein increase, lymphocytic pleocytosis and low glucose lasting 4 weeks or more, [2,3]. subacute meningitis time span is not as well defined but includes those cases from five days to less than four weeks in duration not to mention shorter-lasting presentations with the aforementioned CSF changes [4,5].

Independent on their temporal evolution, both entities distinguish by having typical clinical manifestations, which include headache, nuchal rigidity, photophobia, and variable grades of cognitive impairment. Fever when present is usually lower than 39º Celsius. Unlike acute meningitis, signs, and symptoms in subacute/chronic meningitis follow a more indolent course. In any case during that course, severe consciousness state deterioration, seizures, encephalitis, granulomas and abscesses, hydrocephalus, and other forms of brain, spinal cord, peripheral or cranial nerves can occur [4,6].

Subacute and chronic meningitis are less frequent than their acute counterpart, and that is why we do not know their precise incidence rates [7]. In addition to this, there are other epidemiological aspects which hinder their study including the diverse etiological causes by geographical region [8,9].

Diagnosis for this type of meningitis is extensive and comprise many forms of infectious and non-infectious diseases (Table 1). The most frequent infectious chronic meningitis is caused by Mycobacterium tuberculosis, fungal agents mainly cryptococcus, some virus, syphilis, and Lyme disease. It can also be seen in some parasitic infections such as neurocysticercosis.

Infectious causes	Non infectious
Bacterial: Tuberculosis Syphilis Listeriosis Brucellosis Borreliosis Parameningeal infection	Neoplastic: Carcinomatosis Lymphomatosis Sarcoidosis Sjögren Syndrome Behçet's Disease Systemic Lupus Erythematosus Granulomatous Angiitis Wegener's Granulomatosis Vogt-Koyanagi-Harada Syndrome Migrane with CSF pleocytosis Drug induced meningitis Idiopathic steroid responsive meningitis
Fungal: Cryptococcocal Candidiasis Coccidioidomycosis Hystoplasmosis	
Parasitic: Cysiticercosis Achantoameba Angiostrongylus cantonensis Toxoplasmosis	
Viral: Cytomegalovirus Varicela zoster Epstein Barr Virus Herpes simplex Virus HIV Enterovirus Mumps	

Table 1: Causes of chronic meningitis.

Prevalence is higher in individuals with impaired cellular immunity either from disease or immunosuppressive treatment [4,7]. Patients in this condition may have differences in clinical presentation and evolution compared to immunocompetent hosts.

Diagnosis can be precluded by the protracted clinical course, mild symptomatology, symptomatic treatment, host immunologic state, systemic or other organ involvement. In addition isolating the causative infectious agent can be challenging by conventional means because CSF microbial colonies tend to be low and many of the causative infectious agents have slow growth rates that delay their detection by culture [4]. Therefore, diagnosis requires a meticulous clinical history including exposure, travel and immunologic state history as well as a systemic-oriented physical exam because many of the infectious agents responsible for subacute/chronic meningitis often produce damage to other organs especially the lungs, eyes, skin, and joints. Laboratory and imaging test are always necessary, and pulmonary imaging can be useful in cases with suspicion of tuberculosis or certain mycoses with respiratory pathways of transmission.

Considering that CSF tests and neuroimaging findings are often nonspecific, diagnostic workup most often requires the more sophisticated biomolecular test. Despite this it has been estimated that a third of all chronic meningitis cases will remain without an etiologic diagnosis thus the need of a rational approach [2,5,10-13].

Delay in diagnosis can lead to subsequent delay of pathogen targeted treatment which is related to a higher morbidity and mortality risk [2,3].

Meningeal tuberculosis is the leading cause of chronic meningitis in developing countries and the more severe form of extrapulmonary tuberculosis accounting for 1-5% of these cases with mortality ranging from 7 to 45% [14,15].

In Mexico, there is an incidence of 16 cases per 100 000/year for any tuberculosis, of which 1% is meningeal with an average of 181 cases per year. Even though morbidity has been calculated as 0.1 to 0.4 per 100 000/year, and precise mortality rates are still unknown, estimated in-hospital mortality is 16% [16].

The adult population at risk include people from high tuberculosis prevalence, advanced age, alcoholism, patients taking immunosuppressive drugs, and oncological or HIV infected patients [17-21].

The pathologic changes seen in meningeal tuberculosis are due to basal leptomeningeal inflammation, which can produce damage to the brain parenchyma, cranial nerves, spinal cord, and nerve roots hence de different clinical presentation. Ischemic complications can arise from endarteritis and abscesses, or tuberculomas can be found. Hydrocephalus is another complication that can be resolved by repetitive lumbar puncture or shunting, by repetitive lumbar puncture or shunting, the image with CT and MRI can be essential to detect these pathological conditions and the complications [22-32].

Definitive diagnosis is reached through direct observation of acid-fast bacilli of M. tuberculosis in the CSF or tissue samples, M. Tuberculosis culture or molecular detection methods [33].

Despite adequate treatment, mortality from meningeal tuberculosis ranges between 20 and 50% in different case series. Prognosis strongly depends on the severity of presentation [34-37].

Fungal meningitis is typical infections of immunocompromised patients, especially those with HIV infection even though they also can be found in transplant patients or those receiving immunosuppressive drugs [39]. The most common infectious agents are *C. neoformans, Candida* spp, and the less frequent *C. immitis, H. capsulatum y B. dermatitidis*. The majority of this meningitis are secondary to hematogenous dissemination of a primary lung infection [4,40].

Postmortem studies suggest that CNS mycoses are underestimated and under-diagnosed, which carry an increased mortality rate [41,42]. Candida meningitis mortality varies from 10% to 49%. Similarly, Cryptococcus shows a mortality of up to 40% [43].

There are scarce studies, especially in our country, describing the clinical patterns of presentation of subacute/chronic meningitis, as well as the relationship between said patterns hospital mortality. Additionally, tuberculous meningitis in our background might be over diagnosed as a consequence of proper diagnostic confirmation and high regional frequency.

Based on the considerable variability of presentation between geographical regions and causative agents, it would be beneficial to recognize local clinical patterns to achieve better diagnostic and therapeutic approaches while predicting the mortality risk, helping the physician to make more efficient clinical decisions.

Objective

To describe the clinical patterns of presentation in cases diagnosed as subacute and chronic meningitis of infectious origin in our hospital, as well as determine hospital mortality to later establish the relevance of clinical patterns as mortality predictors.

Materials and Methods

We conducted a retrospective, observational medical record research in the Central Hospital in San Luis Potosí, México, of every adult patient admitted between January 2005 to December 2010 who were diagnosed with any subacute or chronic meningitis.

We included patients older than 15 years old with a complete medical record. Patients with an incomplete medical record, lack of CSF analysis, or previous chronic meningitis diagnosis were excluded.

Amongst the variables to study, we included age, gender, the presence of Diabetes, history of alcoholism, history of neoplasia, HIV infection, immunosuppressive treatment and the time lapse between symptoms start and hospital admission. We documented the presence of one or more signs/symptoms presenting at the beginning of the clinical picture and or during the first 48 hours from admission. These included fever, headache, acute cognitive impairment, changes in awareness, nausea/vomiting, meningism's, cranial nerve dysfunction, papilledema, focal signs, seizures, fever, and death.

We included CSF analysis data, presence or absence of hydrocephalus in imaging tests and if a definitive etiological diagnosis could or could not be achieved. We also considered the time between hospital admission and definite diagnosis, time to beginning of treatment, and antimicrobial used as an initial treatment.

Data analysis

For the statistical analysis, we prosed the use of a statistical test based on Chi-square distribution; nevertheless, the low rate of deaths in this population, we decided to use Fisher's exact test alternatively.

Results

We searched hospital medical records of patients diagnosed with chronic or subacute meningitis, finding 49 eligible files fulfilling our inclusion criteria.

In order of frequency, diagnoses at discharge were tuberculous meningitis (n = 35), chronic meningitis (n = 7), cryptococcal meningitis (n = 5), Histoplasma meningitis (n = 1), and coccidioides meningitis (n = 1), we did not find any cases of meningeal syphilis or meningeal candidiasis. Mean age for the studied population was 43.1 years (range 17 to 81 YO), mostly males (67.3%). The total number of registered hospital deaths was 8, representing 16.3% of all cases.

The most common background risk factor was diabetes mellitus (28.5%), followed by alcoholism (20.4%), all of them in male patients. 18.3% of patient's HIV positive, 6.1% was receiving immunosuppressive drugs, while 4% had a diagnosis of neoplasm.

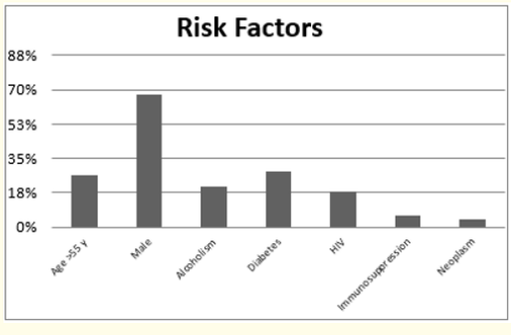

Figure 1

Symptoms at presentation were cognitive impairment (75.5%), headache (73.4%), vomiting (71%), fever (51%) average 38.5ºC, meningismus (48.9%) altered wakefulness (44.8%), focal signs (26%), seizures (26%), and last cranial nerve involvement found in 12 patients (24.4%). The most frequently cranial nerve involved was VI CN (58%), followed by VII, VIII, and II. Papilledema was reported in 2 cases. We must outline that 30% of studied cases presented with a combination of headache, cognitive impairment, and meningismus, all of them in the context of fever.

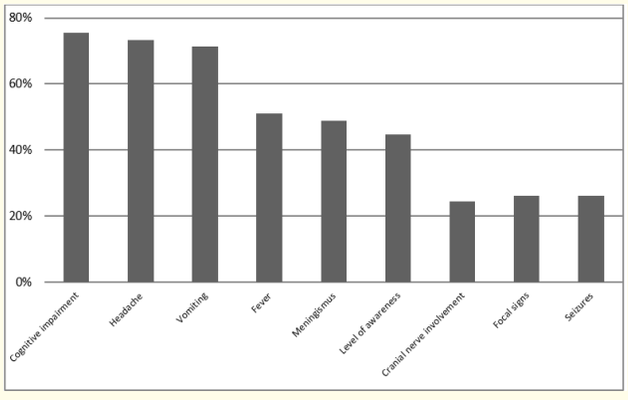

Figure 2: Clinical manifestations.

Average time from the beginning of symptoms to hospital admission was 45.4 days (1 to 270 days).

We encountered lymphopenia in 61% and leucocytosis in 28.5% of all complete blood count analysis. CSF findings showed low glucose in 87.8% of te samples, hyperproteinorraquia in 85.7%, and high leucocyte count in 65.3% (78.1% with lymphocyte predominance). Only 18% presented with acute inflammatory CSF changes, all of the latter with a clinical course longer than five days. We found abnormal images in 41% of patients with chest radiography (n = 43). Hydrocephalus was found in 34% of brain imaging.

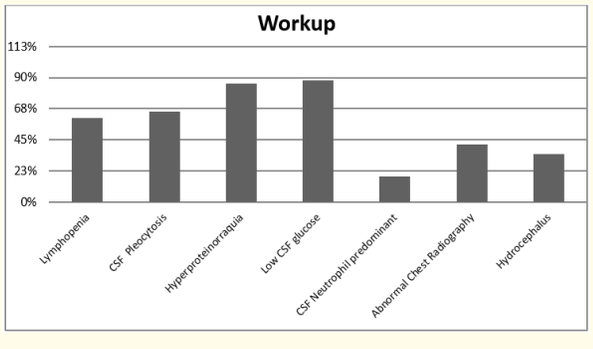

Figure 3

Etiologic diagnostic confirmation by any method was achieved in 30.6% (n = 15), M. tuberculosis being the most frequent (60%), followed by Cryptococcus (26%), and Coccidioides (13%). Average time to final diagnosis was 22.8 days (0 to 75 days), 46% of them in a period longer than 14 days. Time to diagnosis of cryptococcal meningitis was 0.8 days (0 to 2 days), for tuberculous meningitis 20.6 días (4 to 75 days), and of 32 and 75 days for both of the patients with meningeal coccidioidomycosis.

81.6% of patients received empirical treatment in an average time of 7.4 days.

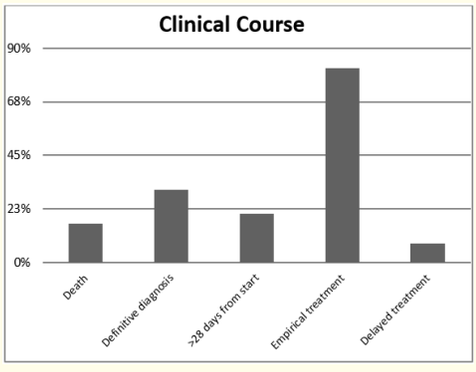

Figure 4

Factors associated with mortality

The results of clinical factors associated with death are listed in table 2.

We observed that from the eight deceased cases 5 were associated to intracranial hypertension, 1 of them also showed brainstem ischemic changes in imaging studies; one death was related to tumoral lysis syndrome, another one to septic shock, and respiratory failure in the remaining case. Even though 75% of the deaths occurred in males, a significant association between mortality and gender was not found (p = 0.5), nor for mortality and age older than 55 years (p = 0.6).

Separately analyzing the relationship of clinical risk factors to mortality, we found a significant association between the latter and patients with neoplasm (p = 0.02), and patients receiving immunosuppressants (p = 0.06). Despite the high prevalence of diabetes mellitus in our population, we did not find any relationship between DM and mortality (p = 0.5), same case for patients with HIV infection (p = 0.5), or alcoholism (p = 0.5).

From all the studied clinical manifestations the highest association was noted for patients with diminished level of arousal (p = 0.06), but no for fever (p = 0.28), seizures (p = 0.88), cognitive impairment (p = 0.7), cranial nerve involvement (p = 0.9), vomiting (0.87), nor for a combination of headache, fever, cognitive changes and meningismus (p = 0.6). Regarding the time from the beginning of symptoms and its association with mortality, we used two dif-

Variable	Death (n=8)	Survivors (n=41)	% Deaths	*p*
Age >55 years	25.0%	26.8%	15.4%	0.6
Gender	75.0%	65.9%	18.2%	0.5
Alcoholism	12.5%	22.0%	10.0%	0.54
Diabetes	25.0%	29.3%	14.3%	0.58
HIV	12.5%	19.5%	11.1%	0.5
Immunosuppression	25.0%	2.4%	**66.7%**	**0.06**
Neoplasm	25.0%	0.0%	**100.0%**	**0.02**
Cognitive impairment	70.0%	75.6%	16.2%	0.7
Vomiting	50.0%	46.3%	17.4%	0.87
Fever	62.5%	43.9%	21.7%	0.28
Meningismus	66.5%	42.3%	20.8%	L
Diminished Arousal	75.0%	39.0%	**27.3%**	**0.06**
Cranial nerve involvement	37.5%	22.0%	25.0%	0.91
Seizures	37.5%	24.4%	23.1%	0.4
Lymphopenia	75.0%	58.5%	20.0%	0.32
CSF Pleocytosis	62.5%	65.9%	15.6%	0.72
Hyperproteinorraquia	87.5%	85.4%	16.7%	0.68
Low CSF glucose	100.0%	85.4%	18.6%	0.32
CSF Neutrophilia	50.0%	12.2%	**44.4%**	**0.02**
Hydrocephalus	75.0%	26.8%	**35.3%**	**0.01**
Without definitive diagnosis	62.5%	70.7%	14.7%	0.81
Clinical course >28 days	50.0%	14.6%	40.0%	**0.04**
Without empirical treatment	12.5%	19.5%	11.0%	0.54
Treatment delay	0.0%	9.8%	0.0%	0.47

Table 2

ferent models, the first one including all cases with an evolution longer than 5 days (without association, p = 0.5) and a second one including only the cases with clinical course longer than 28 days this one showing statistical association (p = 0.04).

We did not find significant evidence between individual laboratory result another tan that documented for predominant neutrophil CSF (p = 0.028) and the presence of hydrocephalus (p = 0.01).

Lacking a definitive etiological diagnosis did not increase mortality (p = 0.6), neither the delaying treatment (p = 0.47) or not receiving any empirical treatment (p = 0.54).

Discussion

Chronic and subacute meningitis are clinical entities associated with high mortality rates, facilitated by difficulties for reaching a precise etiological diagnosis early in the course of the disease. In Mexico, we often lack resources to reach that goal. That is why we must try to comprehend the most frequent clinical patterns of presentation in patients with chronic meningitis in an attempt to identify changes that could orient diagnosis to a particular pathogen.

Medical literature reports that that one third part of patients with this condition will remain without a definitive diagnosis, but in our study, we found that in our population two thirds of the patients were discharged without an etiological diagnosis [35-40].

The inability to reach a proper diagnosis generates delays in treatment start, which in turn can increase mortality, in the same way, that it has been observed in immunocompromised and more prolonged disease duration. In this study, we tried to establish the frequency for hospital mortality under the hypothesis that it would be higher in immunocompromised patients and those with a more prolonged disease, those lacking a precise diagnosis or delays in treatment [45-47]. We also analyzed the different forms of clinical presentations in this heterogeneous group of meningitis to recognize patterns associated to mortality looking to, in the future, shorten the time to treatment start and achieve better outcomes for these patients [48-53,54]. This point is critical because in places where technological and advanced diagnostic tools are unavailable clinical features analysis becomes essential.

In the epidemiological analysis of factors associated with immunocompromise we found a prevalence of DM higher than the general population (28.5% Vs 7.5-12%), from which we can infer that in truth the population carrying DM is more likely to acquire this type of infections, However, it was not possible to establish an association with mortality, same with patients with HIV. On the contrary, patients with immunotherapy and neoplasm showed a significant association with in-hospital mortality; however, this relationship could be masked by the severity of the underlying disease, as well as by the fact that 1 of 3 patients with immunotherapy received this as part of treatment for neoplasia.

We assumed that patients with a longer evolution time would have a higher complication rate and therefore a higher in-hospital associated mortality, however, this relationship could not be demonstrated when cases with 5 days or more of evolution were included, however, when mortality was analyzed in cases with more than 28 days of evolution, the existence of the association was demonstrated.

Possibly because the slowly progressive and indolent natural course of the disease, higher mortality rates could be observed at a longer follow-up time. It would be necessary to design a long-term prospective study in order to verify this statement.

Regarding treatment, we observed that the majority of patients received empirical treatment, initiated in a short time. No relationship was established between delay in treatment initiation or absence of empirical treatment with mortality. There is no way to know if the absence of a relationship derives from adequate and early empirical treatment since no precise diagnosis was established in the majority of patients. It may also be because the evolution of these patients at discharge was not observed. What was observed is that the most used empirical treatment was against tuberculosis, probably because tuberculosis is often the first diagnostic option. The clinical findings associated with in-hospital mortality in this population were mostly those associated with intracranial hypertension, which was ultimately the cause of death in most cases. We mentioned that the patients most likely to die during hospitalization were those with evidence of hydrocephalus as well as patients who presented with altered wakefulness. The association found between CSF with a predominance of polymorphonuclear leukocytes and mortality could be explained by the aggressive inflammatory response of the host, causing significant damage due to pathological processes, including cerebral edema and severe arachnoiditis that could lead to intracranial hypertension. Besides, 5 out of 9 patients with acute inflammatory CSF pattern had a diagnostic confirmation of an agent associated with chronic meningitis, all of these patients having a subacute course of the disease.

Conclusion

The presence of immunocompromise related to immunotherapy and neoplasm, as well as changes in alertness, acute inflammatory pattern in CSF, evolution time greater than 28 days, and clinical findings suggestive of intracranial hypertension, confirmed by the presence of hydrocephalus in imaging studies, are associated with in-hospital mortality in patients diagnosed with subacute / chronic meningitis, thus special attention should be paid to cases presenting with these characteristics, with the intention of improving their prognosis.

The absence of a definitive etiological diagnosis, delay at the beginning of treatment, absence of empirical treatment, or other immunocompromising factors such as alcoholism, DM or HIV infection, were not significantly associated with in-hospital mortality.

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