

CHRONIC MENINGITIS: A STUDY ON EPIDEMIOLOGICAL AND CLINICAL FINDINGS, TREATMENT RESULTS AND PROGNOSIS OF 97 PATIENTS

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Abstract - Central nervous system's disorders including chronic meningitis (CM) have considerable mortality and irreversible complications, and diagnosis and treatment of CM is difficult. In this retrospective study we reviewed epidemiological and clinical findings, treatment results and prognostic factors of 97 patients with CM admitted in Imam Khomeini hospital for the last 10 years. Important etiological factors in this study included: *Mycobacterium Tuberculosis* (8.2%), *Brucellae SP* (5.2%), malignancies (1%) and unknown (85.5%); the sexual ratio was 2:1 (Male/Female) and the most common clinical manifestations were: fever, headache, cranial and motor neuron involvement, seizure and ataxia. Treatment regimens used included antituberculosis agents with or without corticosteroids, in which the prognosis was better in patients who had been treated with antituberculosis agents alone. The mortality rate was 22.7%, which was in accordance with other studies. We suggest using of antituberculosis treatment alone in comparison with antituberculosis and corticosteroid. Last but not least a double blind randomized clinical trial for a longer period is needed to further substantiate the results of this study.

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Key Words: Chronic meningitis, *mycobacterium tuberculosis*, corticosteroid

INTRODUCTION

A large number of infectious and noninfectious diseases can cause the clinical syndrome of chronic meningitis (CM) (1-4).

CM is defined as a syndrome of the neurologic symptoms and signs that either persist or progress clinically and abnormal cerebrospinal fluid (CSF) findings for at least 4 weeks (1-3, 5,6).

There are no pathognomonic clinical features of CM (7). CM can slowly worsen, fluctuate or remain static, and the average duration of symptoms ranges from 17 to 43 months (7,8).

Many diseases that cause a chronic meningeal process can be difficult to diagnose; consequently,

patients with CM often undergo extensive assessments and testing (7,8). However exact diagnosis is difficult and about one third of cases are undiagnosed (9).

Our purpose in this study was to record clinical and laboratory findings, different therapeutic methods and finally prognosis of patients with CM who were admitted at the Imam Khomeini hospital over a 10 year period (1989-1999).

MATERIALS AND METHODS

All patients' medical records classified as meningitis or meningoencephalitis were reviewed first, and data of records with following criteria were used in our study: subacute or chronic onset of a meningitis syndrome (e.g.: headache, cognitive disturbance, lethargy, fever and neck stiffness) with a duration of illness for 4 weeks or longer and in at least one study pleocytosis (6 leukocytes/ml) of the CSF.

Patients' records were excluded from this study if they had any of the following findings:

- 1- Acute meningitis with a duration of less than one month.
- 2- Bacterial meningitis.
- 3- Recurrent acute meningitis.
- 4- A known active neoplasms of CNS or other organs.
- 5- A recent history of craniospinal trauma or a neurosurgical procedures.

Different data including: symptoms, signs, laboratory findings (including CSF studies), results of imaging studies and biopsies, therapeutic methods and outcome of patient at discharge were extracted from patients' records. Finally data were analyzed with SPSS (version 9) software.

RESULTS

With the use of foregoing criteria, we found 97 patients who fulfilled criteria for CM.

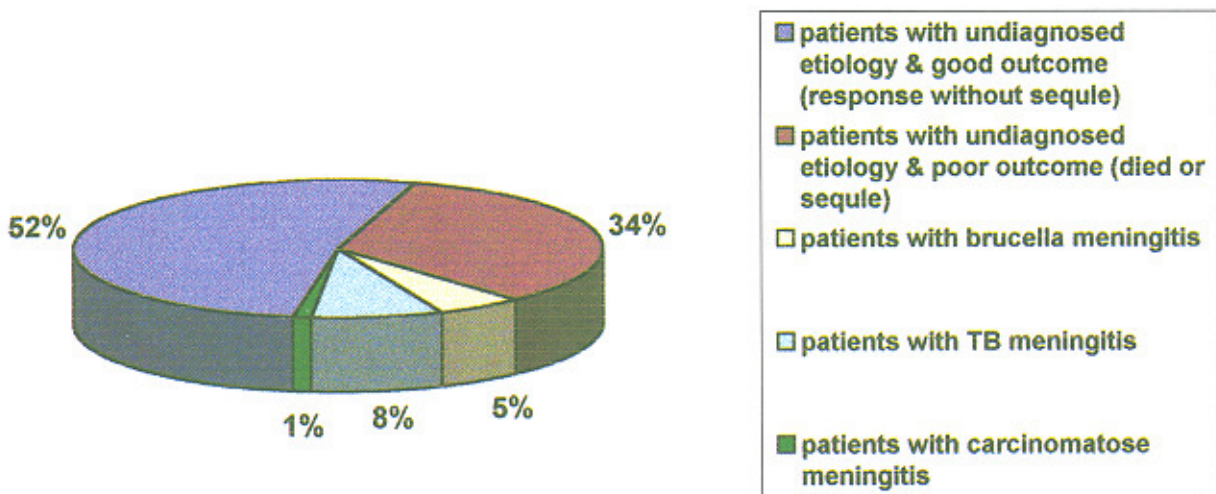


Fig 1. Etiology in 97 patients with chronic meningitis admitted in Imam Khomeini Hospital during 10 years.

Origin

The various etiologies of CM in our patients (pts) are shown in Figure 1.

Etiology could be found in 83 pts (85.5%) and the most common infectious cause among 14 pts with documented etiologies was tuberculous meningitis (8 pts 57.1%).

Patient demographics

The mean age was 28.94 ± 16.16 years (Range : 1 month to 80). Patients with TB meningitis had greater mean age (40.12 ± 26.5) and patients with Brucella meningitis were the youngest group (24.4 ± 12).

Men outnumbered women 2:1 (M = 62 pts, F = 35 pts). Most patients lived in Tehran (44.3%) and others were from Afghanistan (16 pts), west of Iran (12 pts) and other regions of Iran (26 pts).

Signs and symptoms

The common signs and symptoms in our patients are shown in Table 1.

The most frequent complaint was fever (94.8%).

Headache (84.5%), nausea and vomiting and signs of meningeal irritation (78.4%) were also commonly encountered. Cognitive changes had occurred in 72.3% of patients, but severe dysfunction was rare (2.1%). Evidence of focal dysfunction was relatively common. Ataxia was the least common clinical finding in our patients (2.1%).

Radiologic Results

Among 44.3 percent of patients' files which contained chest radiography (CXR) reports, 60.5% (26.8% of total) were normal and pathologic findings

were reported in 39.5% (17.5% of total) of them, usually compatible with tuberculosis. Of the 46 brain CT scan reports, 24 (52.1%) showed normal findings or nonspecific abnormalities, 20 (43.4%) showed hydrocephalus and 2 (4.3%) reported tuberculoma.

Table 1. Signs and symptoms in 97 patients with chronic meningitis at time of initial assessment at Imam Khomeini Hospital

Signs or symptoms	Number	Percent
Fever	92	94.8
Headache	82	84.5
Meningismus	76	78.4
Vomiting	54	55.7
Decreased level of consciousness	53	54.6
Cranial nerve palsy	19	19.6
Focal motor impairment	16	16.5
Seizure	9	9.3
Ataxia	2	2.1

Laboratory findings

The median level of pleocytosis, protein and glucose in CSF of our patients are shown (Table 2).

The median level of CSF pleocytosis was 267.6 cell/mm³. A polynuclear pleocytosis had been shown in 20.6% of patients first on admission but eventually a lymphocytic pleocytosis developed in all patients.

The mean level of CSF pleocytosis was 1320 ± 3347 cell/mm³ in patients with TB meningitis.

The patients with Brucella meningitis had the greatest level of CSF cell count (2296/mm³) and the smallest one was for patients with unknown etiology who responded to treatment with sequele (437.5/ mm³).

The CSF protein level was increased in almost all patients. The median value of CSF protein was 284.7

mg/dl (Range, 0 to 1880 mg/dl).

The median value for CSF glucose was 39.6 mg/dl (range: 5-47.8). The patients with TB meningitis (and 1 patient with carcinomatose meningitis) had the lowest level of CSF glucose and likewise in the patients with Brucella meningitis, median level of CSF glucose was high.

Smear and culture of CSF for bacterial,

mycobacterium and fungal pathogens were negative in 86 patients.

The results of PPD test had been reported in 61 pts (62.9%), among whom 42.6% had negative skin tests.

The mean erythrocyte sedimentation rate (ESR) was 37.5 ± 30.22 mm in 1 hour, with greatest mean level in patients with TB meningitis (44.6 ± 12 mm in 1 hour).

Table 2. Cerebrospinal fluid (CSF) analysis (WBC count, protein and glucose level) in 97 patients with chronic meningitis at time of initial assessment at Imam Khomeini Hospital

Factors	etiology	number	mean	Std. deviation
Leukocytes (no/mm ³)	1	8	132000	3347.82
	2	5	2296	4308.25
	3	1	168	
	4	50	469.28	666.56
	5	22	462.54	579.66
	6	10	437.4	251.19
	total	96	627.62	1465.83
Protein (mg/dl)	1	8	411.8750	467.7449
	2	5	128.0000	180.1597
	3	1	1880.000	
	4	49	217.8571	249.6610
	5	21	391.8095	678.7267
	6	10	204.7000	155.7862
	total	94	284.7340	432.6216
Glucose (mg/dl)	1	8	31.5000	15.9105
	2	5	47.8000	26.0998
	3	1	5.0000	
	4	50	39.2000	16.6513
	5	22	41.0909	20.4378
	6	10	44.6000	27.9531
	total	96	39.6458	19.5346

Table 3. Signs and-symptoms and other characteristics of 97 patients with chronic meningitis stratified by good versus poor outcome.

Sign or symptom	Good outcome (No = 60)		Poor outcome (No = 37)		P
	No.	Percent	No.	Percent	
Motor neurological deficit	4	7	12	32	0.001
Bad condition at time of initial assessment	35	58	30	81	
Unconsciousness at the initial assessment	40	67	30	81	
Empiric therapy with Anti TB	17	28	1	3	0.001
Empiric therapy with Anti TB+ corticosteroid	38	63	32	86	

Table 4. Laboratory values in 97 patients with chronic meningitis at time of initial assessment at Imam Khomeini Hospital stratified by good versus poor outcome

Factor	Good outcome	Poor outcome	All patients	P
CSF glucose (mg/dl)	39.22 (22-56)	40.41 (18-66)	39.64 (5-47.8)	0.23
CSF protein (mg/dl)	236.72 (53-525)	373.48 (239-985)	284.7 (0-1880)	0.032
CSF leukocytes (no/UL)	712.16 (62-1486)	473.47 (97-1043)	627.62 (198-2296)	0.18

Other positive laboratory findings in our patients were:

Positive blood culture for *Brucella Mellitensis* (2 pts).

Positive PCR for *Mycobacterium tuberculosis* in CSF (2 pts).

Positive sputum smear (in at least two specimen) for BK (5 pts).

Chronic granulomatous inflammation compatible with tuberculosis in bone marrow biopsy (1 pt).

Meningeal and leptomeningeal biopsy was done in none of our study patients.

Clinical course and prognostic indicators

Symptoms resolved in 60 of 97 patients (61.9%). Most of them had meningitis with unknown etiology (48 pts, 80%). Outcome was considered good in these patients.

Of the 97 patients, 22 (22.7%) died and 9 remained symptomatic at the time of discharge (with unknown outcome in future). Outcome was considered bad in these patients.

The association between different variables in our patients (common enough for statistical analysis) and outcome is shown table 3 and 4.

Significant statistical association was found between outcome and duration of disease before treatment ($P = 0.053$), CSF protein ($P = 0.032$), evidence of motor neurological deficit ($P = 0.001$), unconsciousness at time of initial assessment ($P = 0.024$) and type of therapeutic regimen ($P = 0.001$).

Treatment

Of the 97 with CM, 88 pts (90.7%) were treated empirically, eighteen pts (20.5%) with antituberculous medications and 70 pts (79.5%) with antituberculous agents and corticosteroids. (Diagnosis of TB meningitis was established in 3 of 18 out anti TB medications latter).

Among 83 pts with undiagnosed condition, 79 had received medications. Fifteen pts (19%) with antituberculous medications (group I) and 64 pts (81%) with anti TB + corticosteroids (group II).

An important finding in our study was that, 14 pts (93.3%) of 15 pts in group I had been improved without any sequelae (and then had a good outcome) but 32 pts (45.7%) out of 64 pts in group II had worsened or died (bad outcome). Therefore, it seems that there was a significant statistical association between corticosteroid therapy and outcome ($P = 0.001$).

DISCUSSION

Chronic meningitis is very uncommon and accounts

for less than 10% of all meningitis cases (9).

Scanty information has been published on the review of cases of CM especially cases of chronic idiopathic meningitis (8).

CM has the widest spectrum of causes among other forms of meningitis. The major infectious causes are tuberculous (TB) meningitis and cryptococcal meningitis (7). In our study 8 pts out of 14 pts with a known etiology had TB meningitis (57.1%).

As discussed previously, diagnosis of many diseases that cause a chronic meningeal process can be difficult and about one third of cases are undiagnosed (7,8,9).

In 1987, Anderson and Willoughby presented one of the largest series to date of cases of chronic idiopathic meningitis. In their study, 28 out of 83 cases of CM, remained undiagnosed (33.7%) (9).

In our 97 pts, the etiology of CM was diagnosed in only 14 pts and 83 remained undiagnosed (88.5%). This high frequency of pts with chronic idiopathic meningitis in our study may be related to:

- Limitted laboratory facilities
- Low socioeconomic level of our study patients
- Early antituberculous medications for patients presenting with chronic meningitis admitted in our hospital. (on the basis of some facts for example : high incidence of tuberculosis in Iran, no evidence of many types of deep fungal infections in immunocompetent pts in Iran and especially high morbidity and mortality of TB meningitis without treatment or delay in treatment).

Male predominance found in our patients is compatible with other studies (1,8,13).

Greater mean age in our patients with TB meningitis (40 years) is contrary to some reports in literature that have found higher frequency of that in children (< 10 years) (9,13).

This finding may be related to lower rate of children admission in our hospital and more important, it may be due to the effect of mass BCG vaccination on prevention of tuberculosis meningitis in children.

Although there are no pathognomic clinical features of CM, but overall the most common complaint in nearly all studies including our current study was fever and headache (1,7,8).

However frequency of some signs and symptoms in our patients was different compared with other studies. For example fever had been reported in 94% of our patients, which is very high compared with Myoclinic report (44%). Ataxia, which was the least common presentation in our study (2.1%), had been reported in 44% of Myoclinic patients.

The laboratory investigation for CM can be quite extensive. In Myoclinic study of 37 chronic meningitis patients who ultimately underwent leptomeningeal biopsy there were 2295 CSF tests, 1289 serologic tests, 401 radiologic studies, 1152 other studies and 82 extraneural biopsies. Only 157 of these tests (3.3%)

were abnormal (7), which is very extensive in comparison with our study. However, as discussed earlier, the limitations of laboratory investigations in our study, only led to high incidence of undiagnosed CM and had no effect on outcome of patients.

In our study, CSF was abnormal in all patients and neuroimaging was abnormal in 48% which is relatively compatible with some other studies (6,8).

On the basis of our study, most cases of CM with definite diagnosis had a good outcome (12 pts = 85.7%).

Also among 79 patients with undiagnosed etiologies, most cases had a nonfatal course (49 pts = 62%).

But overall short-term outcome in our patients with undiagnosed etiology was not good (22 pts died, 22.7% and 9 pts remained symptomatic = 10.3%), in comparison with other studies (77% good outcome in Myoclinic report and 89.3% good outcome in Anderson report).

We think that this difference might be due to the use of a different and unique empiric therapy in study patients (i.e.: corticosteroids plus antituberculous medications for relatively large group of patients, 64 pts = 65.7% and no longterm follow up of patients in our study).

Anderson and Willoughby discussed the difficulty of accurately determining the duration of symptoms in chronic meningitis. For example one patient had resolution after 6 years and in another patient the condition was worse at follow-up after 12 years of initial symptoms (8). On the other hand in some recent studies, implied that it is usually of short duration (10,12).

Decisions about empiric therapy in CM depend on severity of illness, whether a presumptive cause can be established, and toxicity of the proposed empiric therapy (7). Antituberculous (anti TB) medication should be the first choice for empiric treatment of CM (4,7,12).

Empiric therapy with anti TB medication was helpful in our patients (14 of 15 patients, 94.4%, had improvement), which is contrary to Anderson report (14 of 28 patients, 50%, responded to antituberculous medications) (9). We think it may be discussed by early treatment of our study patients.

Combination therapy with the antituberculous agents and corticosteroids that has been used in 64 of 79 patients (79.5%) with undiagnosed CM (who have received empiric therapy) has not yet been reported in literature.

We have found significant difference in eventual outcome between patients treated with antituberculous agents alone (14 of 15 patients, 94.4%, had a good outcome) and patients who had received antituberculous and corticosteroid medications (35 of 64, 54.7%, had a good outcome). Thus considering this statistically significant difference and no evidence of

usefulness of such combination in the treatment of patients with undiagnosed CM in literature we suggest that in the first step empiric therapy should include antituberculous agents only.

None of our study patients had received amphotericin or corticosteroid agents as empiric therapy. These medications have different efficacy on outcome of patients with chronic undiagnosed meningitis according to other studies.

Charleston and Anderson have found relatively good response among patients treated with corticosteroids (7 of 17 patients, 41%, had complete improvement and 4 of 17 patients 23% had relative response but eventually had died).

We suggest empiric therapy with corticosteroids in chronic idiopathic meningitis only after repeated negative laboratory investigations for infectious diseases and no response to first choice of empiric therapy (antituberculous), particularly where HIV infection and or tuberculosis are more prevalent.

In Conclusion chronic meningitis can be produced by many different infectious and noninfectious causes.

Although sensitivity and specificity of laboratory findings are usually low, but an informed approach to chronic meningitis helps assure timely diagnosis and optimal management.

Finally physician's awareness in encountering chronic meningitis with a high percentage of unknown etiology and its empirical therapy remains the cornerstone of management in this part of the world.

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Chronic meningitis

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