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TEACHING REVIEW

J. Hildebrand
M. Aoun

Chronic meningitis: still a diagnostic challenge

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J. Hildebrand · M. Aoun
Institut Jules Bordet
rue Héger-Bordet 1
1000 Bruxelles, Belgium
Tel.: +32-2/541-3706
Fax: +32-2/541-3295

Abstract Chronic meningitis is characterized by a progressive, subacute onset of lepomeningeal disease and persisting cerebrospinal fluid (CSF) abnormalities such as elevated protein level and pleocytosis for at least one month. The array of aetiologies is very wide comprising non-infectious (carcinomatous, systemic disease, toxic) and infectious (classic and opportunistic pathogens). The evaluation encompasses a careful history, complete physical examination and laboratory tests. The specific diagnosis may remain a challenge in some cases. Algorithms for the differential diagnosis are provided for both immunocompetent and immunocompromised patients.

Key words chronic meningitis · differential diagnosis · algorithms · AIDS · systemic diseases

Introduction

Chronic meningitis is usually defined as a predominant leptomeningeal disease with CSF-inflammatory cells persisting for one month or longer. Only primary meningeal diseases will be reviewed in this article. Meningeal reaction to parenchymal brain abscess or to parameningeal lesions will not be considered. Compared with acute meningitis the onset of the reviewed diseases is more progressive and their course more protracted. In most patients, several weeks or months may elapse from initial manifestation to diagnosis [32, 33]. The neurological deficits are usually less dramatic than in acute bacterial meningitis, the signs of meningeal irritation are milder and may even be absent. Fever, when present, is usually below 39 °C.

Infection, tumour, systemic disease, and toxic reaction may cause chronic and sub-acute meningitis (Table 1). However, it is essential to keep in mind that the distinction between acute and chronic meningitis is primarily based upon the clinical presentation and the duration of CSF-inflammatory changes, and that agents causing predominantly chronic or sub-acute meningitis may have an acute presentation associated with initial CSF polymorphonuclear pleocytosis. Clinical features of CNS-infection depend not only upon the "seed" but also upon the "soil". Immune state, age, prior sensitisation influence the incidence, the severity and the rate of evolution of leptomeningeal infections.

Aetiology, clinical presentation and CSF changes in main chronic and sub-acute meningites

A retrospective survey performed in New Zealand between 1967 and 1983, in a population without risk factors, identified 83 cases of chronic meningitis [3]. During the same period, acute bacterial or viral meningites were diagnosed in 1,000 patients. The causative agent was identified in 55 patients (66 %) and the most common causes were tuberculosis (60 %), carcinoma (13 %) and *Cryptococcus neoformans* (11 %). This distribution is probably fairly representative of most European countries. But the epidemiology of chronic meningitis shows striking differences in geographic distribution. For in-

Table 1 Chronic meningitis

Definition:	Subacute onset of symptoms (≥ 1 month) Clinical signs of meningoencephalitis CSF abnormalities : elevated protein concentration and pleocytosis	
Etiologies:		
Infectious causes		*Non infectious causes*
Bacterial:	Tuberculosis	Neoplastic meningitis
	Syphilis	Sarcoïdosis
	Listeriosis	Sjögren syndrome
	Brucellosis	Behçet's disease
Fungal:	Cryptococcosis	Systemic lupus erythematous
	Candidiasis	Granulomatous angiitis
	Coccidioidomycoses	
	Histoplasmosis	
Parasites:	Cysticercosis	
	Acanthamoeba	
	Angiostrongylus cantenensis	
	Toxoplasmosis	
Viral:	Cytomegalovirus	
	Varicella zoster virus	
	Epstein Barr virus	
	Herpes simplex virus	
	Human immunodeficiency virus	
	Enterovirus	
To differentiate from recurrent meningitis – Post traumatic – Parameningeal abscess or tumor – Rechallenge with neurotoxic drug		

stance, coccidioidomycosis is endemic in North, Central and South America while histoplasmosis may also occur in Africa, India and South East Asia.

Infectious causes

Tuberculous meningitis

After a substantial and steady decline, the incidence of tuberculosis is increasing in several European countries owing to the AIDS epidemic and immigration from countries where the incidence of the disease is high. In countries with still low incidence of tuberculosis, tuberculous meningitis tends to occur mainly in adults and is often the only active manifestation of the disease. It often results from the seeding of mycobacteria to the subarachnoid space from an old tuberculous focus. In contrast, in younger patients, tuberculous meningitis is associated with active progressive disease. The mean prodromal stage consisting of apathy, anorexia, malaise, intermittent headaches, lasts two to three weeks, but sometimes a few months may elapse before the diagnosis is made. Cranial nerve lesions are seen in about 40 % of the cases [12].

Typical CSF examination reveals tens to hundreds of cells predominantly lymphocytes. Protein level is of the order of 100 mg/100 ml but may be much higher if there is a spinal block. Glucose is decreased often markedly and lactic acid is increased. Definite diagnosis requires bacilli demonstration by Ziehl-Neelson stain or culture on Löwenstein medium, which may require several weeks [28]. PCR is a rapid, sensitive and specific test, and may remain positive several weeks following treatment initiation [22]. Tuberculin reaction may be negative, especially in immunosuppressed patients.

Other infectious meningites

Most sub-acute or chronic meningites reviewed here may resemble tuberculous meningitis, clinically or by CSF changes, and are part of its differential diagnosis.

Fungal meningitis

Cryptococcus neoformans is the most common cause of chronic infectious meningitis in immunosuppressed patients. Clinical and CSF abnormalities often resemble tuberculous meningitis. However, large granulomas mimic expanding lesions with intracranial hypertension and papilloedema. In immunosuppressed patients, CSF cell count and protein may be normal. *Cryptococcus neoformans* may be demonstrated in the CSF by India ink stain in 30 to 50 %. The most rapid and sensitive diagnostic test is the detection of cryptococcal antigen in CSF and serum.

Candida meningitis usually has a chronic evolution. Most cases have been reported in patients treated with antibiotics, corticosteroids or other immunosuppressors [30].

Lyme disease (Bannwarth disease)

Meningitis is the most common neurologic manifestation caused by *Borrelia burgdorferi*, a spirochete transmitted by ixodic ticks. In 40 % of the patients, there is a history of erythema migrans, the initial manifestation of the disease (stage 1).

Weeks to months later, patients may develop migratory arthritis. About 15 % of untreated patients progress to neurological involvement that includes meningitis, radiculoneuritis and cranial nerve neuritis (stage 2). The meningitis is fluctuant, causing headaches, photophobia and nausea. Stiff neck is found in up to 20 % of the cases. CSF is characterized by mild elevation of mononuclear cell (about 100 cells/mm^3) and protein with frequent oligoclonal IgG bands. CSF glucose is normal. Years after the primary infection, some patients may develop signs of encephalopathy and polyneuropathy (stage 3). However, at this stage, the meningeal reaction (CSF pleocytosis and elevated protein) is clinically silent in most patients [8, 9].

The diagnosis of neuroborreliosis is based on the demonstration of elevated levels of specific immunoglobulins by ELISA. IgM antibodies are first detected at 3–4 weeks after infection (peak 6–8 weeks) and IgG at 8–12 weeks (peak 6 months) [5].

During recent decades, a PCR that detects *Borrelia burgdorferi* DNA in CSF has been evaluated extensively. The sensitivity was low and the usefulness of CSF PCR test on a routine basis is not established [21, 25].

Neurosyphilis

Today neurosyphilis is largely linked to AIDS. About 15 % of patients infected with HIV have serological evidence of syphilis and 1 % have neurosyphilis. Chronic inflammatory meningeal reaction characterized by dozens of cells predominantly lymphocytes, elevation of protein around 100 mg/100 ml with possible presence of oligoclonal IgG bands, and normal glucose is common to all forms of neurosyphilis, and 95 % of the cases occur during the first year following primary infection. Meningeal neurosyphilis may remain asymptomatic or resemble any acute viral meningitis with malaise, fever, stiff neck and headache. Patients may also develop cranial nerve deficits, especially of VIIth and VIIIth nerves, and cerebral infarcts (meningovascular syphilis). The diagnosis of active neurosyphilis is based on previously described CSF inflammatory changes and serological tests in blood and CSF [17]. CSF-VDRL (Veneral Diseases Research Laboratory) test is highly specific but false-positive reaction may be due to blood contamination, high CSF protein or autoimmune disease. Fluorescent treponemal antibody (FTA) test is even more specific, but because of its sensitivity cannot be used in CSF. The diagnosis of syphilis is therefore based on specific blood test (FTA) and reactive CSF-VDRL. Occasionally, CSF-VDRL may be negative in patients with neurosyphilis and AIDS [25].

Brucellosis

Brucellosis occurs preferentially in individuals in close contact with cattle or who ingest unpasteurised milk. Systemic manifestations follow an undulant course including fever, sweats, malaise and headaches. Clinical signs include lymphadenopathy and splenohepatomegaly. Neurological manifestations occur in a minority of patients and consist of chronic meningitis or meningoencephalitis that may be accompanied by cranial nerve palsy [17]. CSF changes closely resemble those of tuberculous meningitis with low glucose level in at least 50 % of the cases. Clinical diagnosis is confirmed by serological or PCR tests that are both specific and sensitive. CSF cultures are seldom positive [1].

Meningitis in AIDS patients

HIV-1 is associated with a cohort of neurological complications that are either related to the HIV-1 infection or caused by opportunistic infections or neoplasm. Chronic meningeal reaction occurs in all these conditions, and inflammatory CSF changes may be ascribed to HIV infection only after exclusion of secondary pathogens and tumour.

Opportunistic infectious agents causing meningitis include viruses such as CMV, HSV, VZV, EBV, fungi such as *Cryptococcus neoformans*, Candida species, *Coccidioides immitis* and *Histoplasma capsulatum* and bacteria such as *Listeria monocytogenes*, *Treponema pallidum* [7, 16].

Primary lymphoma is the main brain tumour, occurring in 1 to 3 % of AIDS patients. The tumour is usually multicentric, of B-cell type, and produces a meningeal reaction characterized by a moderate T-type lymphocytosis (< 50 cells/mm^3), moderate increase of proteins, oligoclonal IgG fractionation (in about 50 % of the cases), and usually normal glucose level [16]. PCR is positive for EBV in up to 100 % of the patients.

A small percentage (1 to 2 % of AIDS patients) develops acute "aseptic" meningitis with headaches, meningism and occasional cranial neuropathy and encephalopathy. This reaction may occur early in the course of the disease, sometimes before seroconversion. About half of HIV-1 carriers develop, during seropositive and ARC stages, a chronic or recurrent meningeal pleocytosis (< 30 cells/mm^3), and a mild CSF-protein increase (< 100 mg/100 ml). In most patients, this meningeal reaction remains asymptomatic and does not predict any specific neurological complication.

Miscellaneous agents

- Most bacteria including *Listeria monocytogenes* cause acute purulent meningitis. However, in some patients, CSF changes in *L. monocytogenes* meningitis may mimic tuberculous meningitis by the predominance of lymphocytes and low glucose.
- Bacteria identification may be jeopardized by antibiotic pre-treatment. In the CSF of most of these patients polymorphonuclear predominance usually persists [4].
- CNS-cysticercosis is a common cause of chronic meningitis. Clinical features range from mild headaches to meningism and hydrocephalus. Eosinophiles are frequently found in the CSF. Cerebral cysticercosis is common in Mexico, central and south America, and Southern and Eastern Asia, and in immigrants from these countries [6].
- CNS infection by *Toxoplasma gondii* is frequent in immunosuppressed patients, and causes brain abscesses or diffuse encephalitis. CSF changes are char-

acterized by moderately elevated protein levels without mononuclear pleiocytosis. The parasite may be demonstrated in centrifuged CSF sediment by Giemsa staining. A PCR has been developed for early diagnosis [10, 19, 20].
– Sub-acute or chronic meningitis may complicate intraventricular shunts or reservoirs, coagulase-negative staphylococcus and propioni bacterium acnes are the most common agents [34].

Neoplastic leptomeningitis

The clinical presentation of neoplastic leptomeningitis reflects a widespread multifocal involvement of the central and peripheral nervous system, and results from any combination of the following symptoms and signs : confusional state, raised intracranial pressure, cognitive disorders, epileptic seizures, meningism (rarely predominant), cranial nerve and spinal root palsies.

Leptomeningeal metastases occur in four main categories of malignant diseases : solid tumours, leukemias, non-Hodgkin's lymphomas and primary brain tumours.

1. Symptomatic meningeal carcinomatosis is observed in up to 8 % of the patients with solid tumours. The main primaries are breast and lung carcinoma and melanoma [27]. In about 90 % of the cases, the diagnosis of the primary malignancy precedes that of meningeal metastases. Exceptionally, carcinomatous meningitis may reveal the presence of a cancer [23].
2. Meningeal leukaemia occurs primarily in acute leukaemias of childhood. In lymphoblastic leukaemia, the incidence was 70 % before prophylactic therapy, and still reaches 5 to 10 % despite prophylaxis. In myelogenous leukaemia, the incidence of meningeal involvement varies from 30 to 50 % of the cases.
3. Up to 20 % of patients with non-Hodgkin's lymphoma develop meningeal metastases. The main risk factors are high histological grade and advanced clinical stage.
4. In primary brain tumours, meningeal cerebro-spinal seeds mainly occur in childhood. They are found in over 30 % of medulloblastomas, 10 to 20 % of pineal and suprasellar germinomas, and 10 % of anaplastic ependynomas. In adults, cerebro-spinal invasion is rare in gliomas (≤ 3 %) and tends to be correlated with high grade. In primary CNS lymphomas, meninges are involved in about 20 % of the cases. Primary meningeal gliomatosis is exceptional [29].

The diagnosis of neoplastic leptomeningitis is based on the demonstration of neoplastic cells in the CSF. Repeating lumbar puncture and examining large samples (5 ml) of CSF increases the percentage of positive examination. The recognition of malignant cells may be difficult in lymphomas where the monoclonality (usually of B-type) is masked by T-type reaction. The identification of glial neoplastic cells may be also difficult and immunocytochemical staining of glial and fibrillary proteins may help to identify such cells. Other CSF changes, seen in neoplastic leptomeningitis, include high protein, often contrasting, with moderate increase in lymphocytes and low glucose levels sometimes close to zero. Determination of human chorionic gonadotrophin and α-foetoprotein is useful in the diagnosis of germ-cell tumour dissemination. The CSF concentrations of β-glucoronidase, lactate dehydrogenase (LDH) isoenzyme, and β2-microglobulin are frequently increased in leptomeningeal metastases, but lack specificity. Elevated concentration of carcinoembryogenic antigen favours carcinomatous meningitis.

Contrast-enhanced MRI demonstrates leptomeningeal involvement in nearly 70 % of the patients and may often show concomitant parenchymal metastases. In an appropriate clinical setting, typical MRI changes are increasingly accepted as evidence of neoplastic meningitis, even if malignant cells cannot be demonstrated in the CSF.

The prognosis of carcinomatous meningitis is dismal with an overall median survival of 2 to 4 months in solid tumours and of more than 6 months in lymphomatous meningitis. Increasing the repertoire of available drugs for intrathecal administration, and applying new approaches such as gene therapy and immunotoxins may attenuate in the future the death sentence of carcinomatous meningitis [24].

Systemic diseases

Sarcoidosis

In most patients, CNS-sarcoidosis is preceded or is combined with systemic lesions: lung (70 %), skin (30 %), and lymphatic glands (25 %). However, isolated neurosarcoidosis does exist. A granulomatous leptomeningitis is almost invariably found in patients with CNS-sarcoidosis. When symptomatic, this meningitis follows a chronic, often remittent course. The predominantly basal lesion locations involve cranial nerves, optic chiasma, and hypothalamus. CSF is characterized by a moderate increase of lymphocytic cells, increase of protein with occasional oligoclonal fractionation of IgG. CSF-glucose is moderately decreased in less than 20 % of the cases [31].

Collagen-vascular diseases

These diseases usually combine visceral disorders, rush and arthritis related to inflammatory lesions of blood

vessels. Neurological disorders are common. Symptomatic or asymptomatic leptomeningeal reaction occurs in several syndromes: primarily in Behçet's disease, Sjögren's syndrome, lupus erythematosus, and primary granulomatous CNS angiitis.

Behçet's disease

Behçet's disease is relatively common in Japan and the Mediterranean area. It is characterized by relapsing uveitis, genital and oral ulcers, and involvement of other organs. Sub-acute or chronic, usually febrile, meningoencephalitis is with cerebral thrombophlebitis the most common manifestation of neuro-Behçet. CSF pleocytosis is predominantly lymphocytic but may mimic in some cases purulent meningitis by a high percentage of polynuclear cells. Protein increase is moderate and CSF-glucose is normal. Oligoclonal bands may be found [2, 11, 13].

Sjögren's syndrome

In this dry eyes and mouth syndrome, CNS complications are fairly rare, they may consist of an aseptic meningoencephalitis. CSF is characterised by pleocytosis made of plasmatocytes, macrophages and lymphocytes. Oligoclonal bands have been reported [14].

Systemic lupus erythematosus

This multi-organ disease preferentially affects young women. Cerebral lupus occurs in 25 to 50% of the patients causing psychosis, seizures and dementia. Chronic meningitis is rare (about 1%). CSF is characterised by increased lymphocyte count, and oligoclonal fractionation in one patient out of two. Glucose is normal, and low glucose is considered to be characteristic of transverse myelitis.

Primary granulomatous CNS angiitis

This disease, restricted to the CNS, is due to granulomatous changes in cerebral blood vessels. Headaches of progressive severity, a prominant clinical manifestation, may be combined with manifestation of encephalopathy including cognitive changes. CSF is characterized by lymphocytosis and normal glucose levels. Angiography demonstrates arterial beading in only 10 to 30% of the cases, and the diagnosis is best confirmed by meningeal biopsy [15].

Toxic meningeal reaction

Meningeal reaction to chemicals (anticancer drugs, antibiotics, analgesics, anaesthetics or contrast dyes) is here considered briefly because the aetiology is usually obvious, and because the onset of meningism is often acute. Toxic meningitis may produce fever and the main differential diagnosis is the rare infectious meningitis caused by septic lumbar puncture. Chemical meningitis also occurs in pituitary apoplexy due to infarction or haemorrhage of a pituitary tumour, and in ruptured epidermoid cyst or craniopharyngioma. In patients with undiagnosed neoplasms, the diagnosis may be difficult.

Differential diagnosis

The identification of meningitis aetiology is primarily based on the examination of CSF and other tissues, which includes direct stain, cultures on aerobic, anaerobic, Löwenstein (mycobacteria) and Sabouraud (fungi) media, determination of specific antibodies and antigens possibly using PCR technology. However, even with the use of modern techniques, the aetiology of chronic meningitis remains unknown in a substantial percentage of patients. Figures 1 and 2 summarize the main manifestations of chronic meningitis in the immunocompromised and the non immunocompromised patients. These algorithms allow a highly accurate prediction of the most likely aetiology. Empirical treatment is indicated in patients in a serious clinical condition, with progressive neurologic deficits, and immunosuppression. In such cases, the therapeutic likelihood is based on:

a) CSF changes other than the identification of germs or neoplastic cells
   - Markedly decreased CSF-glucose characterises tuberculous, carcinomatous and cryptococcal meningitis. Patients with non-purulent and low CSF-glucose should be treated for tuberculous meningitis until proven otherwise.
   - Discrepancy between high protein (> 200 mg/100 ml) and moderate lymphocyte count (< 50 cells/mm^3) favours carcinomatous meningitis in patients with low CSF glucose.
   - Presence of eosinophils in the CSF favours parasite infection.
   - Polynuclear predominance suggests bacterial meningitis in patients pre-treated with antibiotics or Behçet disease in an appropriate clinical setting.
   - Oligoclonal IgG fractionation may occur in Borreliosis, neurosyphilis, primary CNS lymphoma, sarcoidosis and collagen-vascular diseases.
b) Clinical course of the meningitis
   - Relatively rapid (sub-acute) course favours the diagnosis of tuberculous, or neoplastic meningitis.
   - Fluctuating chronic course is common in Brucellosis, Borreliosis, Behçet disease and collagen-vascular diseases.
c) Neurological and systemic symptoms and signs

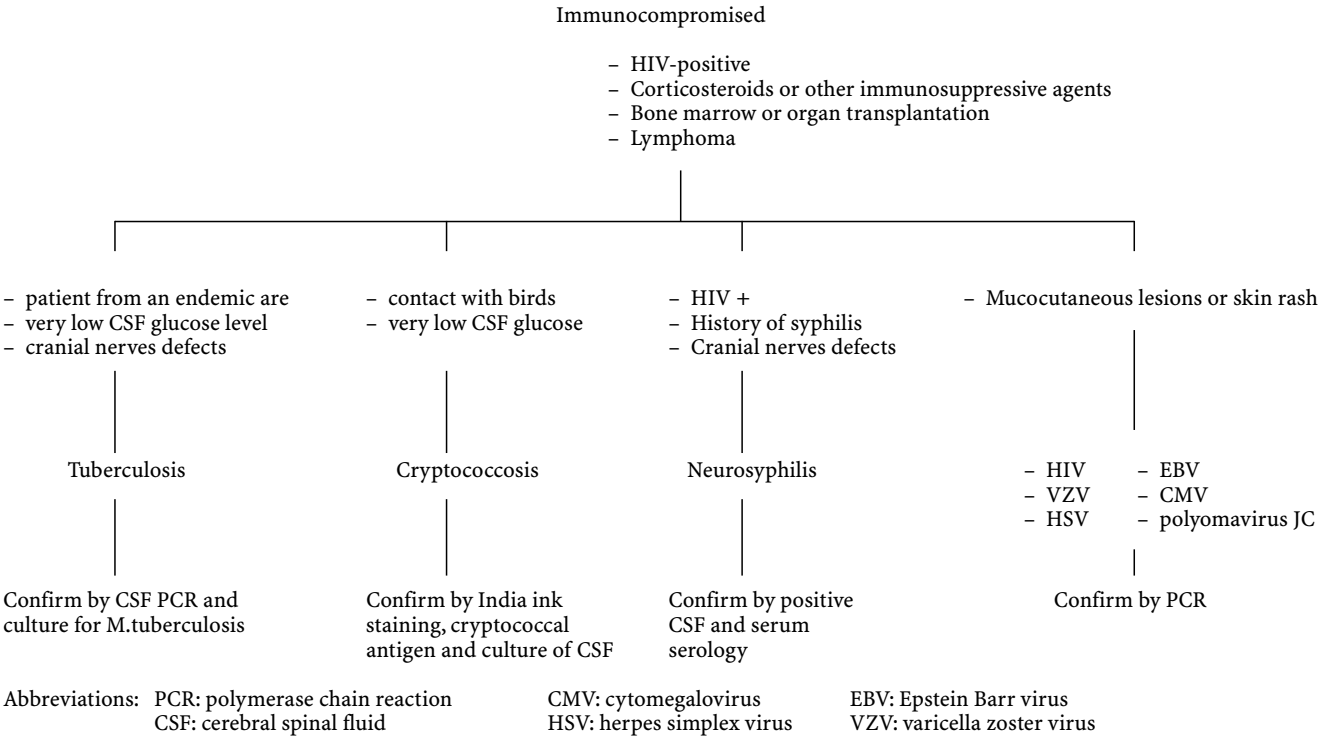

Fig. 1 Chronic meningitis

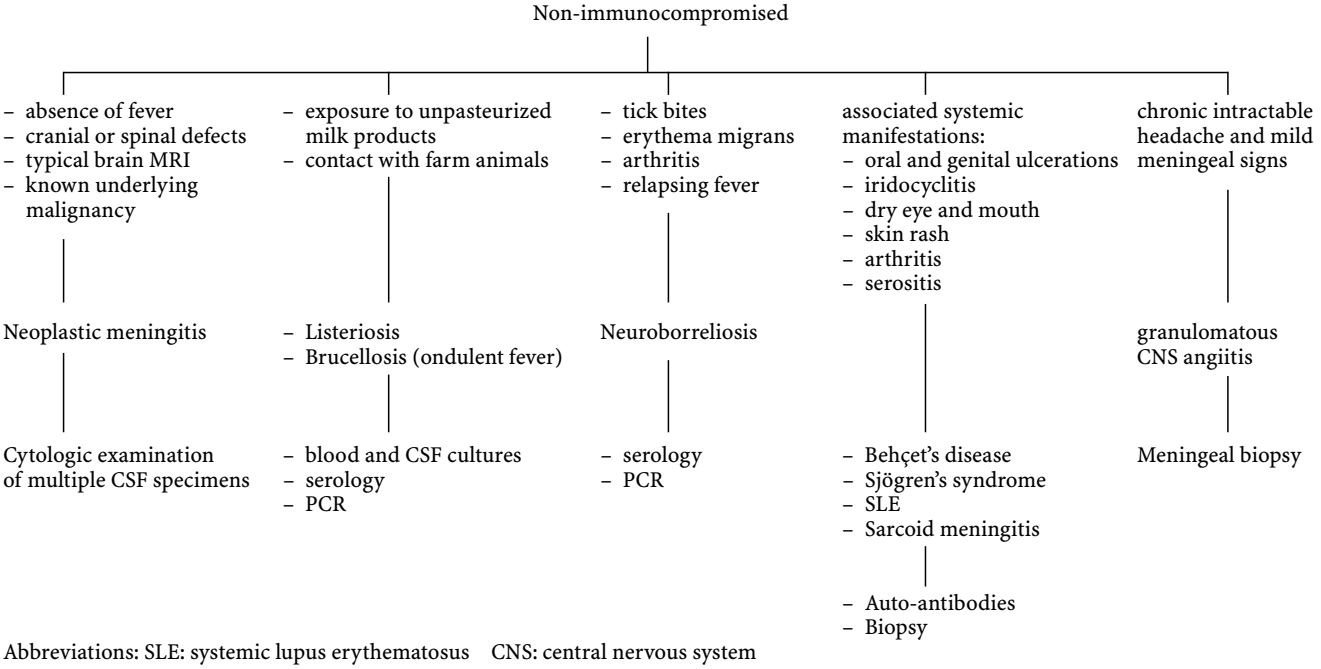

Fig. 2 Chronic meningitis

- Radicular pain and palsy suggest carcinomatous meningitis.
- Migratory erythema and arthritis point to Lyme disease.
- Undulant fever, lymphoadenopathy and hepatosplenomegaly are evocative of Brucellosis.
- Visceral disorders, rush and arthritis are common in collagen-vascular diseases. Genital and oral ulcers characterise Behçet disease, and dry eyes and mouth the Sjögren's syndrome.

d) Radiological investigations
- Chest imaging is abnormal in 70 % of patients with sarcoidosis, and it is often contributive in patients with CNS metastases and infections.
- On MRI, nodular leptomeningeal enhancement and concomitant parenchymal metastases favour the diagnosis of neoplastic meningitis. Linear enhancement is more common in infectious meningitis.

e) Laboratory investigations and biopsy
- Serum specific antibodies and cultures may contribute to the identification of the infectious agent.
- Serum auto-antibodies are very useful in the diagnosis of collagen-vascular diseases. They include Sjögren's syndrome antibodies A and B (SSA and SSA) and double strand antinuclear antibodies in the diagnosis of lupus erythematosus.
- Biopsy is the most contributive diagnostic test in primary granulomatous CNS angiitis, and in sarcoidosis confined to the nervous system. Salivary gland biopsy may be diagnostic in Sjögren's disease and sarcoidosis.

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