Multidisciplinary approach in the investigation and treatment of chronic meningitis: A systematic review of the literature and current guidelines

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ABSTRACT

This study presents a systematic review on chronic meningitis, an inflammatory condition of the membranes surrounding the brain and spinal cord, with potential for severe neurological complications and risk of fatality if not properly treated. We employed a rigorous methodology, including a comprehensive review of the literature in reputable databases such as PubMed, Scopus, Web of Science, Cochrane Library, and Embase. Inclusion and exclusion criteria were stringent to ensure the selection of relevant and high-quality studies. The analysis of selected studies revealed several underlying causes of chronic meningitis, ranging from infections to malignant neoplasms, autoimmune disorders, chemical meningitis, and parameningeal infections. Clinical manifestations are diverse and may include persistent headache, hydrocephalus, cranial nerve damage, spinal nerve damage, and cognitive alterations. Accurate diagnosis is crucial and is based on cerebrospinal fluid

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(CSF) analysis, involving a series of laboratory and microbiological tests. The importance of a multidisciplinary approach in the management of chronic meningitis is emphasized, which should involve clinicians, neurologists, microbiologists, and pathologists. Early identification of the specific cause and implementation of appropriate treatment are fundamental to improving clinical outcomes. Empirical therapy may be necessary in cases of uncertain diagnosis, but adjustments should be made based on clinical evolution and test results. We conclude that interdisciplinary collaboration and continuous updating of clinical practice are essential for the effective management of chronic meningitis. Future research should focus on the development of faster and more accurate diagnostic techniques, as well as more effective therapeutic strategies, aiming to significantly improve the quality of life of patients affected by this debilitating condition.

Keywords: Chronic Meningitis, Multidisciplinary Approach, Diagnosis, Treatment.

INTRODUCTION

Chronic meningitis is an inflammatory condition of the meninges that involves the persistence of symptoms and clinical signs for a period of more than four weeks 11. Unlike acute meningitis, which has a sudden onset and rapid evolution, chronic meningitis presents an insidious and progressive clinical picture, which often hinders its diagnosis and clinical management [1]. This condition can be caused by a variety of etiological agents, including bacterial, viral, fungal, and parasitic infections, as well as non-infectious causes such as autoimmune diseases and neoplasms [9].

The diagnostic and therapeutic approach to chronic meningitis requires a multidisciplinary approach, involving professionals from different areas of medicine, such as neurologists, infectious disease specialists, rheumatologists, immunologists, and oncologists [8]. This complexity is due to the diversity of causative agents and the varied clinical presentations, which may include headache, persistent fever, cognitive alterations, focal neurological signs, and systemic symptoms [7]. Accurate identification of the etiologic agent is crucial to direct the appropriate treatment, which can range from the use of specific antibiotics and antifungals to the administration of immunosuppressants in cases of autoimmune etiology [9].

Although there are established clinical guidelines and consensus for the management of acute meningitis, specific recommendations for chronic meningitis are less clear and often based on case studies or case series, given the rarity and heterogeneity of the disease [1,6]. Systematic review of current literature and critical analysis of existing guidelines are essential to consolidate knowledge, identify gaps and inconsistencies, and propose more effective and integrated approaches.

This article aims to conduct a systematic review of the literature on the multidisciplinary approach in the investigation and treatment of chronic meningitis, synthesizing the available evidence and current guidelines. It seeks to provide a comprehensive overview of best clinical practices, identify areas that need further research and development, and propose recommendations that can improve the clinical outcomes of patients affected by this complex and challenging condition.

The relevance of this study lies in the potential to positively impact clinical practice by offering health professionals an up-to-date and well-founded resource for the diagnosis and management of chronic meningitis, promoting a more effective and integrated approach to patient care.

METHODOLOGY

The methodology has been carefully structured to comprehensively examine the crucial aspects of the disease. Initially, a detailed literature review was conducted covering the epidemiology, etiology, pathogenesis, clinical manifestations, differential diagnoses, and treatment strategies of chronic meningitis. To identify relevant studies, renowned scientific databases such as PubMed,

Scopus, Web of Science, Cochrane Library and Embase were used. Specific search terms used included "chronic meningitis", "multidisciplinary approach", "differential diagnosis", "treatment", "epidemiology", "etiology" and "guidelines".

To ensure the relevance and quality of the studies included in the review, strict inclusion and exclusion criteria were established. Inclusion criteria included studies that directly addressed epidemiological, etiological, pathogenic, clinical, diagnostic, and therapeutic aspects of chronic meningitis, including systematic reviews, meta-analyses, observational studies, controlled clinical trials, and clinical guidelines, as long as they were fully available and published within the last 20 years. Studies that were not fully available, did not have relevant data, or did not fit the specific objectives of this review, as well as duplicate publications, were excluded.

The selected studies were critically analyzed and synthesized to identify patterns, knowledge gaps, and controversies in the field of chronic meningitis. The analysis included an assessment of underlying molecular mechanisms, such as chronic inflammatory immune responses and genetic and environmental factors associated with the disease. The different diagnostic approaches, including laboratory tests, imaging and molecular methods, as well as the therapeutic strategies involving pharmacological, surgical and multidisciplinary support approaches, were also explored.

Ethical considerations were rigorously observed, including the review and synthesis of secondary data, with particular attention to the potential presence of publication bias and the inherent limitation of reliance on published data. A formal statistical analysis was not performed, given the predominantly literature review and critical analysis of existing studies. The manuscript underwent peer review to ensure data accuracy, clarity of presentation, and compliance with ethical and methodological standards, providing a solid framework for the comprehensive analysis of chronic meningitis and the identification of future research directions.

In addition to the electronic databases, relevant books were consulted to provide a comprehensive and in-depth view on specific topics of chronic meningitis, such as neurobiology, pharmacology, and clinical manifestations. The books used were selected based on their relevance and authority in the field of medicine and neuroscience, ensuring a solid foundation of knowledge for the review. This meticulous and comprehensive methodology aims to provide a detailed and integrated analysis of multidisciplinary approaches in the investigation and treatment of chronic meningitis, identifying current practices and highlighting areas in need of further research and development.

LITERATURE REVIEW

Chronic inflammation of the meninges, which include the pia mater, arachnoid, and dura mater, can cause profound neurological disability and, if not properly treated, can be fatal [4]. Chronic

meningitis is diagnosed when a typical neurological syndrome persists for more than four weeks, accompanied by an ongoing inflammatory response in the cerebrospinal fluid (CSL), evidenced by a leukocyte count greater than 5/μL [3]. The causes of chronic meningitis are varied, and effective treatment depends on the accurate identification of the underlying etiology [4].

There are five main categories of diseases responsible for most cases of chronic meningitis. The first category includes infections of the meninges, which can be caused by bacteria, viruses, fungi, or parasites [9]. The second category is malignant neoplasm, where malignant tumors can invade or compress the meninges, leading to inflammation [11]. Autoimmune inflammatory disorders constitute the third category, with diseases such as systemic lupus erythematosus and sarcoidosis causing inflammation of the meninges [4]. The fourth category is chemical meningitis, which can occur due to the introduction of irritants into the subarachnoid space [4]. Finally, the fifth category encompasses parameningeal infections, where infections located in areas adjacent to the meninges, such as in nearby bones or soft tissues, can spread and cause meningeal inflammation [4].

PHYSIOPATHOLOGY

The neurological manifestations of chronic meningitis are determined by the anatomical location of the inflammation and its consequences. The main manifestations include persistent headache, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes, which may occur alone or in combination [12]. The combination of these symptoms indicates a wide spread of the inflammatory process along the cerebrospinal fluid (CSL) pathways [7]. In some cases, the presence of an underlying systemic disease suggests a specific agent or class of agents as the probable cause [9].

The diagnosis of chronic meningitis is usually established when the clinical picture leads the physician to examine the CSL for signs of inflammation [1]. The LCS is produced by the choroid plexus of the cerebral ventricles and crosses narrow foramina into the subarachnoid space, which surrounds the brain and spinal cord [4]. It circulates around the base of the brain and over the cerebral hemispheres, being reabsorbed by arachnoid villi that protrude into the superior sagittal sinus [4]. This flow is a route for the rapid spread of infections and other infiltrative processes to the brain, spinal cord, and cranial and spinal nerve roots [5]. Inflammation can spread from the subarachnoid space to the brain parenchyma through the arachnoid sheaths that surround the blood vessels that penetrate the brain tissue (Virchow-Robin spaces) [4, 5].

Specific clinical manifestations of chronic meningitis include a variety of signs and symptoms, such as chronic headache, neck or back pain and stiffness, personality changes, altered mental status, facial weakness, double vision, hearing loss, limb weakness and numbness, and urinary retention or incontinence [4, 7]. These symptoms reflect the extent and location of meningeal

inflammation [7]. For example, the stimulation of the nociceptive nerve fibers of the meninges by the inflammatory process results in headache and cervical or lumbar pain [7]. Obstruction of the CSL pathways can cause hydrocephalus and signs of elevated intracranial pressure, such as headache, vomiting, apathy, drowsiness, gait instability, papilledema, visual loss, and cranial nerve palsy [VI 4].

Cognitive and behavioral changes may result from vascular damage due to inflammation around blood vessels in the subarachnoid space, causing infarctions [3]. Inflammatory deposits, often prominent around the brainstem and cranial nerves, as well as along the lower surface of the frontal and temporal lobes, characterize basal meningitis [4]. This is often manifested by multiple cranial neuropathies, with decreased vision, facial weakness, hearing loss, diplopia, and sensory or motor abnormalities in the oropharynx, as well as decreased sense of smell and facial sensation [4,7].

Spinal meningitis may involve lesions of the motor and sensory nerve roots when they cross the subarachnoid space and penetrate the meninges, manifesting as various radiculopathies, with combinations of radicular pain, sensory loss, motor weakness, and urinary or fecal incontinence [5]. Chronic inflammation can cause thickening of the meninges and pinching of the nerve roots, a condition known as pachymeningitis, which can reach and damage the spinal cord, resulting in myelopathy [3]. Patients with slowly progressive involvement of various cranial and/or spinal nerve roots are likely to have chronic meningitis [12]. Electrophysiological tests may be useful to determine the involvement of these nerve roots [4].

In some patients, the presence of evidence of systemic disease may provide clues about the underlying cause of chronic meningitis [12]. A thorough history of travel, sexual practices, and exposure to infectious agents is critical [12]. Infectious causes are often associated with fever, malaise, anorexia, and signs of localized or disseminated infection outside the nervous system [7]. This is particularly relevant in immunosuppressed patients, such as those with HIV infection, in whom chronic meningitis may present without headache or fever [4]. Non-infectious inflammatory disorders may produce systemic manifestations before manifesting as meningitis [3]. Carcinomatous meningitis may or may not be accompanied by clinical evidence of primary neoplasia [5].

APPROACH TO THE PATIENT WITH CHRONIC MENINGITIS

The presence of chronic headache, hydrocephalus, cranial neuropathy, radiculopathy, and/or cognitive decline in a patient suggests the need for lumbar puncture (LP) to look for evidence of meningeal inflammation [2,4]. Sometimes, the diagnosis is made when a contrast-enhanced examination (computed tomography (CT) or magnetic resonance imaging (MRI) shows extravasation of the contrast agent into the meninges [5]. Meningeal enhancement is always worrisome, except in cases of dural reinforcement after LP, neurosurgical procedures, concussion, or spontaneous cerebrospinal fluid (CSL) [leakage 4]. Once chronic meningitis is confirmed by examination of the CSL, efforts should

be directed to identify the cause, which may involve further analysis of the CSL, diagnosis of underlying systemic infection or non-infectious inflammatory disorder, or histopathological examination of biopsy specimens of the meninges [4].

There are two clinical forms of chronic meningitis: one with chronic and persistent symptoms and the other with distinct and recurrent episodes of the disease [12]. In cases of recurrent episodes, all symptoms, signs, and parameters of meningeal inflammation of the CSL resolve completely between episodes, either spontaneously or in response to specific treatment [12]. Possible causes include Mollaret's meningitis, often caused by herpes simplex virus (HSV) type 2 infection; chemical meningitis, due to episodic extravasation of epidermoid tumor, craniopharyngioma, or cholesteatoma contents into the CSL; and primary autoimmune inflammatory conditions, such as Vogt-Koyanagi-Harada syndrome, Behçet's syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis, IgG4-related disease, and hypersensitivity to drugs with repeated administration of the offending agent [4, 5].

Epidemiological history is crucial in the diagnosis of chronic meningitis and can guide the selection of laboratory tests [1]. Relevant aspects include history of tuberculosis or exposure; recent epidural injection that may lead to epidemics of fungal meningitis caused by Exserohilum rostratum; travel to areas endemic for fungal infections, such as California's San Joaquin Valley and southwestern U.S. states for coccidioidomycosis, Midwestern states for histoplasmosis, and southeastern states for blastomycosis; travel to the Mediterranean region or ingestion of imported unpasteurized dairy products (Brucella); time spent in endemic areas for Lyme disease; exposure to sexually transmitted infections (syphilis); exposure of an immunocompromised host to pigeons and their excreta (Cryptococcus neoformans var. gatti); gardening (Sporothrix schenkii); ingestion of undercooked meat or contact with domestic cats (Toxoplasma gondii); residence in Thailand or Japan (Gnathostoma spinigerum), Latin America (Paracoccidioides brasiliensis) or the South Pacific (Angiostrongylus cantonensis); residence in rural areas with exposure to raccoons (Baylisascaris procyonis); and residence in Latin America, the Philippines, Sub-Saharan Africa, or Southeast Asia (Taenia solium/cysticercosis) [1, 3, 4, 5, 7].

The presence of focal brain signs in patients with chronic meningitis suggests the possibility of brain abscess, parameningeal infection, neoplasia, or vasculitis [5]. Identification of the causative agent requires a detailed analysis of the CSL and other investigations, such as culture and Gram staining, polymerase chain reaction (PCR) tests, and detection of specific antibodies, as well as imaging tests such as CT and MRI to assess the extent of meningeal inflammation and identify possible foci of infection or neoplasms [4].

IMAGING AND CEREBROSPINAL FLUID ANALYSIS

For patients with suspected chronic meningitis, imaging is essential, especially if elevated intracranial pressure (ICP) is suspected [1, 4]. Before proceeding with lumbar puncture (LP), it is crucial to perform neuroimaging to rule out the presence of expansive lesions, cerebral edema, or blockage in ventricular cerebrospinal fluid (CSL) flow, which may increase the risk of brain herniation [4]. Magnetic resonance imaging (MRI) and computed tomography (CT) are indispensable tools in these cases [3]. They can identify meningeal uptake, parameningeal infections such as brain abscesses, spinal cord entrapment due to neoplasms, inflammations or infections, and nodular deposits in the meninges or nerve roots, which may indicate malignant neoplasms or sarcoidosis [4].

In addition, angiography can be used to detect signs of cerebral arteritis in patients with chronic meningitis who have a stroke [7]. In cases of obstructive hydrocephalus, direct ventricular drainage may be necessary [7]. Patients with open cerebrospinal flow pathways and elevated ICP due to deficiency in CSF absorption by the arachnoid villi can usually undergo LP safely, and it may even be therapeutic [3,11]. However, repetitive or continuous lumbar drainage may be required to avoid sudden deterioration and death from elevated ICP [3]. In some cases, such as cryptococcal meningitis, elevated levels of life-threatening ICP can occur without enlargement of the ventricles [4].

Cerebrospinal fluid (CSL) analysis is critical for the diagnosis of chronic meningitis [1, 2]. LCS pressure should be measured initially, and specimens should be sent to the laboratory for a series of tests, including bacterial, fungal, and tuberculosis culture, VDRL testing, total and differential cell counts, Gram staining, and measurement of glucose and protein levels [1, 2]. Fresh preparations for fungi and parasites, preparation with India ink, cultures for bacteria and fastidious fungi, cryptococcal antigen testing, immunoglobulin oligoclonal bands, and cytology should be performed [2, 3]. Other LCS-specific tests or blood cultures and cultures may be ordered based on clinical history, physical examination, or preliminary LCS [3 results].

Serological testing and polymerase chain reaction (PCR) to identify DNA sequences specific to the suspected pathogen can speed up diagnosis. PCR for ribosomal RNA (rRNA)16s is useful for detecting a wide range of bacterial causes of meningitis, especially in partially treated [meningitis6,8,9]. The 18s and 28s rRNAs can aid in the detection of fungal species9. In suspected fungal infections, the determination of β-glycans can be a valuable complementary test [9]. With technological advancements, next-generation metagenomic unbiased sequencing is becoming widely available, representing an efficient method for diagnosing difficult cases [4].

In most cases of chronic meningitis, mononuclear cells predominate in the LCS [11]. When neutrophils prevail after three weeks of illness, etiologies such as Nocardia asteroides, Actinomyces israelii, Brucella, Mycobacterium tuberculosis (in 5 to 10% of initial cases), various fungi (such as Blastomyces dermatitidis, Candida albicans, Histoplasma capsulatum, Aspergillus spp.,

Pseudallescheria boydii, Cladophialophora bantiana) and non-infectious causes such as systemic lupus erythematosus (SLE) and exogenous chemical meningitis should be considered [4, 5, 9]. The presence of eosinophils or their predominance in a mononuclear cellular response may indicate parasitosis, mycoses, neoplastic diseases, or other inflammatory processes [4].

It is often necessary to increase the number of complementary tests when the initial investigation does not reveal the etiology [1]. Repeated samples of large volumes of lumbar CSL may be necessary to establish the diagnosis of certain infectious and malignant causes of chronic meningitis [3]. Lymphomatous or carcinomatous meningitis can be diagnosed by examining sections of a cell block formed by centrifugation of the sediment of a large volume of CSL [10]. Flow cytometry for malignant cells may also be useful in suspected cases of carcinomatous meningitis [4]. Diagnoses of fungal meningitis may require large volumes of LCS for sediment culture9. When conventional lumbar puncture is unproductive, cervical cistern puncture may be useful to obtain CSF close to the basilar meninges, and ventricular fluid may appear sterile in cases of active infection in the lower lumbar space [4].

LABORATORY INVESTIGATION AND DIAGNOSTIC APPROACH TO CHRONIC MENINGITIS

In the investigation of chronic meningitis, in addition to the examination of the cerebrospinal fluid (CSL), it is crucial to identify underlying diseases. Tuberculin skin tests, chest X-ray, urine examination and culture, complete blood count and differential count, renal and hepatic function tests, alkaline phosphatase, erythrocyte sedimentation rate, antinuclear factors, anti-Ro and anti-La antibodies, rheumatoid factor, and IgG4 level are frequently indicated [1, 4]. In some cases, it is necessary to investigate thoroughly in search of a systemic focus of infection, especially in cases of fungal disease or tuberculosis [11,12]. Computed tomography (CT) or magnetic resonance imaging (MRI) scans of the chest, in addition to sputum scans, may be useful [4]. Abnormalities can be detected by bronchoscopy or transthoracic needle biopsy [4]. Although tuberculin skin testing has limited specificity and sensitivity, γ-interferon release tests can be used to diagnose latent tuberculosis [4]. Liver, bone marrow, or lymph node biopsy can be diagnostic in cases of miliary tuberculosis, disseminated mycosis, sarcoidosis, or metastatic malignancy [3]. Positron emission tomography with 18F-fluorodeoxyglucose may be valuable to identify systemic sites for biopsy in patients with suspected carcinomatous meningitis or sarcoidosis, when other tests do not provide information [5]. Genetic testing can identify mutations responsible for rare monogenic autoinflammatory disorders [5].

If CSL analysis is not diagnostic, meningeal biopsy should be considered in patients with severe disability, need for chronic ventricular decompression, or progressive disease [1, 4]. Coordination between surgeon, pathologist, microbiologist, and cytologist is essential to obtain an adequate sample

and perform appropriate cultures, as well as histological and molecular studies, including electron microscopy and PCR [7, 8]. The positivity rate of meningeal biopsy is higher when contrast-enhanced regions are selected on MRI or CT [5]. With current microsurgical techniques, it is possible to access most areas of the basal meninges for biopsy by means of limited craniotomy [5]. In a series of cases, MRI demonstrated meningeal enhancement in 47% of patients undergoing meningeal biopsy; Biopsy of a contrast-capturing region was diagnostic in 80% of cases, while biopsy of non-uptake regions was diagnostic in only 9% [1,4]. The most common diseases identified were sarcoidosis (31%) and metastatic adenocarcinoma (25%) [4].

In about 33% of cases, the diagnosis remains unknown, despite careful evaluation of the CSL and possible extraneural sites of disease [4,12]. Several microorganisms that cause chronic meningitis can take weeks to be identified in cultures [9]. In enigmatic cases, the options are determined by the extent of the clinical deficits and the rate of progression [4]. It is prudent to wait for the results of cultures if the patient is asymptomatic or if symptoms are mild and not progressive [1]. However, in many cases, progressive neurological deterioration occurs, requiring rapid treatment [5]. Ventriculoperitoneal shunts can relieve hydrocephalus, but the risk of propagating an undiagnosed inflammatory process to the abdomen should be considered [4].

Establishing the diagnosis of the etiologic agent is essential, as there are effective treatments for many causes of chronic meningitis [1,2]. If the disorder is left untreated, progressive damage to the central nervous system (CNS) and cranial nerves and roots is likely to occur [5]. On certain occasions, empirical therapy should be instituted when all attempts at diagnosis have failed [10]. Generally, empiric therapy in the United States consists of antimycobacterials, amphotericin for fungal infection, and/or glucocorticoids for non-infectious inflammatory causes [4]. It is important to direct the empirical treatment of lymphocytic meningitis to tuberculosis, especially when associated with low glucose levels in the CSL, as the untreated disease can be devastating in a few weeks [5]. Long-term therapy with tumor necrosis factor inhibitors and programmed anti-cell death 1 (PD-1) may reactivate tuberculosis; These patients who develop chronic meningitis should be treated empirically with antituberculosis therapy if the etiology is uncertain [10,12]. In the Mayo Clinic series, the most effective empirical treatment was the administration of glucocorticoids instead of antituberculosis therapy [4]. When using glucocorticoids empirically, caution should be exercised with transient responses to treatment, as some infectious etiologies (such as tuberculosis and cysticercosis) and non-infectious etiologies (such as lymphoma) may respond temporarily to glucocorticoid monotherapy [4]. Carcinomatous or lymphomatous meningitis can be difficult to diagnose initially, but becomes evident over time [1, 12].

Chronic meningitis is not uncommon in the course of HIV infection [12]. Pleocytosis and mild meningeal signs are frequent at the beginning of HIV infection, with occasional persistence of low-

grade meningitis [12]. Toxoplasmosis usually manifests as intracranial abscesses, but can also be associated with meningitis [9]. Other causes of chronic meningitis in AIDS include infection with Cryptococcus, Nocardia, Candida or other fungi, syphilis, and lymphoma [3]. Toxoplasmosis, cryptococcosis, nocardiosis, and other fungal infections are important etiological factors to be considered in individuals with immunodeficiency states unrelated to AIDS, even those caused by immunosuppressive agents [3,4]. Due to the increased risk of chronic meningitis and the attenuation of clinical signs of meningeal irritation in immunosuppressed individuals, it is necessary to examine the LCS in the presence of any persistent headache or unexplained change in mental status [4].

RESULTS AND DISCUSSION

A systematic review of the literature on chronic meningitis revealed a wide range of etiologies, clinical manifestations, diagnostic approaches, and therapeutic strategies. The main causes of chronic meningitis include infections, malignancies, autoimmune disorders, chemical meningitis, and parameningeal infections [1, 4]. Chronic meningeal infections can be caused by a variety of pathogens, including bacteria such as Mycobacterium tuberculosis, fungi such as Cryptococcus neoformans, viruses such as herpesvirus, and parasites such as Toxoplasma gondii [9]. Malignant tumors, including carcinomas and lymphomas, can invade the meninges, causing chronic inflammation [11]. Autoimmune diseases such as systemic lupus erythematosus (SLE) and sarcoidosis often present chronic meningitis as one of the manifestations [4,5]. The introduction of irritants into the subarachnoid space can result in persistent meningeal inflammation, while infections located in areas adjacent to the meninges, such as in the bones or nearby soft tissues, can spread and cause meningeal inflammation [2, 4, 12].

The clinical manifestations of chronic meningitis are varied and depend on the anatomical location of the inflammation and its consequences [4,7]. The main symptoms include persistent headache, hydrocephalus, cranial neuropathies, radiculopathies, and cognitive or personality changes [7,12]. These symptoms reflect the extent and location of meningeal inflammation [7]. The stimulation of the nociceptive nerve fibers of the meninges by the inflammatory process results in headache and cervical or lumbar pain [7]. Obstruction of the cerebrospinal fluid (CSL) pathways can cause hydrocephalus and signs of elevated intracranial pressure, such as headache, vomiting, apathy, drowsiness, gait instability, papilledema, visual loss, and cranial nerve palsy [4,12]. Cognitive and behavioral changes may result from vascular damage due to inflammation around blood vessels in the subarachnoid space, causing infarctions [3]. Basal meningitis, characterized by prominent inflammatory deposits around the brainstem and cranial nerves, is often manifested by multiple cranial neuropathies [4].

For the diagnosis of chronic meningitis, analysis of LCS 4 is essential. LCS pressure should be measured initially, and specimens should be sent to the laboratory for a series of tests, including bacterial, fungal, and tuberculosis culture, VDRL testing, total and differential cell count, Gram staining, and measurement of glucose and protein [levels 4]. Fresh preparations for fungi and parasites, preparation with India ink, cultures for bacteria and fastidious fungi, cryptococcal antigen testing, immunoglobulin oligoclonal bands, and cytology should be performed [4]. Serological testing and polymerase chain reaction (PCR) to identify DNA sequences specific to the suspected pathogen can speed up diagnosis [6, 8]. PCR for ribosomal RNA (rRNA)16s is useful for detecting a wide range of bacterial causes of meningitis, especially in partially treated [meningitis6,8,9]. The 18s and 28s rRNAs can aid in the detection of fungal species9. In suspected fungal infections, the determination of β-glycans can be a valuable complementary test [9].

In cases where the initial analysis of the CSL does not reveal the etiology, it may be necessary to increase the number of complementary tests [1]. Repeated samples of large volumes of lumbar CSL may be necessary to establish the diagnosis of certain infectious and malignant causes of chronic meningitis 4. Lymphomatous or carcinomatous meningitis can be diagnosed by examining sections of a cell block formed by centrifugation of the sediment of a large volume of LCS [10,12]. Flow cytometry for malignant cells may also be useful in suspected cases of carcinomatous meningitis [4]. Diagnoses of fungal meningitis may require large volumes of LCS for sediment [culture4,9]. When conventional lumbar puncture is unproductive, cervical cistern puncture may be useful to obtain CSF close to the basilar meninges [4].

Establishing the diagnosis of the etiologic agent is essential, as there are effective treatments for many causes of chronic meningitis [9]. If the disorder is left untreated, progressive damage to the central nervous system (CNS) and cranial nerves and roots is likely to occur [5]. In some situations, it may be necessary to institute empirical therapy when all attempts at diagnosis have failed [4, 8]. Generally, empiric therapy in the United States consists of antimycobacterials, amphotericin for fungal infection, and/or glucocorticoids for non-infectious inflammatory causes [4]. It is important to direct the empirical treatment of lymphocytic meningitis to tuberculosis, especially when associated with low glucose levels in the CSL, as the untreated disease can be devastating in a few weeks [5]. Long-term therapy with tumor necrosis factor inhibitors and programmed anti-cell death 1 (PD-1) may reactivate tuberculosis; These patients who develop chronic meningitis should be treated empirically with antituberculosis therapy if the etiology is uncertain [10,12]. Response to treatment should be closely monitored, and adjustments should be made as needed, based on clinical progress and test results.

The results of this review highlight the complexity of diagnosing and treating chronic meningitis. The multidisciplinary approach, involving clinicians, neurologists, microbiologists and

pathologists, is essential for the accurate identification of the etiology and the implementation of an effective treatment. Early identification and appropriate treatment can prevent serious complications and significantly improve the prognosis of patients with chronic meningitis.

CONCLUSION

The present systematic review of chronic meningitis offers a comprehensive understanding of the various etiologies, clinical manifestations, diagnostic approaches, and therapeutic strategies associated with this complex condition. We evidence that chronic meningitis can result from a variety of infectious agents, malignant neoplasms, autoimmune disorders, chemical reactions, and parameningeal infections. Each of these etiologies presents specific diagnostic and therapeutic challenges, requiring a careful and detailed approach.

Cerebrospinal fluid (CSL) analysis remains the cornerstone of diagnosis, with complementary methods such as polymerase chain reaction (PCR) and flow cytometry playing crucial roles in identifying difficult-to-detect pathogens and malignant cells. The variability in clinical manifestations, ranging from persistent headache to cognitive changes and cranial neuropathies, underlines the importance of a comprehensive and multidisciplinary clinical evaluation.

The findings reinforce the need for an empirical approach, especially in cases where an accurate etiological diagnosis is not quickly achieved. Empirical therapy, adjusted to the most likely clinical suspicions, can prevent disease progression and minimize irreversible damage to the central nervous system.

We conclude that early identification and appropriate treatment of chronic meningitis are essential to improve clinical outcomes. Interdisciplinary collaboration is critical to the successful management of this condition, highlighting the importance of continuous updates in clinical practice based on emerging evidence. Future research should focus on the development of faster and more accurate diagnostic techniques, as well as therapeutic strategies that can be implemented more effectively and with less associated morbidity. Advancement in these areas will have a significant impact on improving the quality of life of patients affected by chronic meningitis.

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