Aseptic Noninfective Meningitis: Etiologic Survey

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Abstract

Aseptic non infective meningitis are rare but represent a veritable diagnostic challenge to the clinician because their clinical and cerebrospinal fluid profile are similar to those of classic infectious meningitis. The most frequent etiologies of these meningitis are: systemic diseases, drugs, and neoplasms but several other exceptional causes can also be found. The aim of this review is expose the different possible causes to evoke and discuss in patient with aseptic meningitis (infectious causes excluded).

INTRODUCTION

Definitions

Meningitis is defined by the existence of an acute or chronic inflammation of the meninges covering brain and spinal cord. The most frequent causes of these affections are infections: viral, bacterial and uncommonly fungal meningitis.

Absence of an infectious agent in the cerebrospinal fluid definite “noninfective meningitis” or “aseptic meningitis” [1]. This meningitis can be acute, chronic or recurring especially in systemic diseases and can occurs with or without anomalies of the cerebrospinal fluid (CSF). The chronicity of meningitis is defined by the persistence of clinical signs and/or symptoms of meningitis for more than four weeks, and it occurs for less than 10% of all the cases of meningitis [2,3].

Recurrent meningitis are defined by as at least two clinically similar episodes of meningitic syndrome with an interval of clinical and cerebrospinal fluid normalization [2,3].

The most frequent etiologies of these noninfective meningitis are: connective tissue diseases, systemic or cerebral primitive vasculitis, drugs, neoplasms, and systemic granulomatosis [1]. Other exceptional causes can be listed: diabetes, physical nervous aggression and traumatism, neurological surgery, AIDS, and some connectivitis-like syndromes. However, it should be noted that in about 30% of the cases, no cause is identified inspite of an extensive etiologic investigation; Thus it is called “idiopathic meningitis” which is generally chronic and/or recurring [2,3].

In this review of the literature, we expose the different possible causes to evoke and discuss in patient with aseptic meningitis (infectious causes excluded).

ETIOLOGIES OF ASEPTIC NONINFECTIVE MENINGITIS

The most common causes are systemic diseases, drugs and cancers. Cerebral thrombosis are assimilated to systemic diseases [1,2]. Less frequently other causes can be also seen: granulomatosis, angitis, brain traumatisms or surgery and certain exceptional specific clinico-pathological entities.

Systemic diseases and vasculitis

Neurological involvement is common in systemic inflammatory diseases and cerebrospinal manifestations represent serious complications reflecting disease activity. Their prognosis is universally poor.

Aseptic meningitis is reported in systemic lupus erythematosus[4,5], mixed connective tissue disease [4], overlap syndrome [4], Sjogren’s syndrome [1,4,6], Behçet’s disease [1,7,8], sarcoidosis[1,9], polychondritis[10,11], multiple sclerosis [12], systemic vasculitis, especially those affecting small vessels such as granulomatosis with polyangiitis (formerly Wegener’s granulomatosis)[1,13], Vogt-Koyanagi-Harada syndrome [14] and primary angiitis of central nervous system.

In systemic disorders, neurological complications including aseptic meningitiscan be the result of multiple mechanisms: intracranial vascular lesions (vasculitis and thrombosis), specific autoantibodies to neuronal antigens, ribosomes, and phospholipids, and inflammation related to local cytokine production [15-17]. Anti-U1RNP antibody was founded in 93% of patients with connective tissue diseases and aseptic meningitis [4]. Cerebrospinal fluid findings in these cases showed elevated levels of IgM, IgA, and IgG indexes resulting of intrathecal immunoglobulin synthesis [17]. As well as Interleukin-6 activity and anti-neuronal antibody (anti-N) are significantly elevated in the CSF [17].

Aseptic meningitis is also rarely noted in patients with Sweet syndrome [18,19], Still’s disease [20,21], cerebral vein thrombosis [1,22], Kikuchi-Fujimoto disease [23,24], and...
Drug-induced meningitis

Drug-induced aseptic meningitis (DIM) is a rare adverse effect of some drugs. They represent a veritable diagnostic challenge to the clinician [49-51] because their clinical and cerebrospinal fluid profile are similar to those of infectious meningitis [51,52]. The incidence of DIM is unknown.

The most common medications inducing aseptic meningitis include: antibiotics, non-steroid anti-inflammatory drugs, muromonab-CD3 (OKT3), and intravenous immunoglobulin [49-59].

Other cases of aseptic meningitis has been reported with carbamazepine [60], sulfasalazine [61-63], serotonin uptake inhibitors [64], azathioprine [65], hepatitis B vaccination [66], measles-mumps-rubella vaccination[67]ranitidine [68], salicylate overdose [69], lamotrigine [70], leflunamide [71], spinal anesthesia/intrathecal administration of bupivacaine [72,73], intramuscular methotrexate [74], ergot agents[75], and biologic agent (monoclonal antibodies/anti-TNF-α/epidermal growth factor receptor [EGFR] inhibitor) [76-80].

Latency from drug intake to the development of aseptic meningitis varies from few minutes to several months, and prior exposure to the drug can be noted in 3-45% of cases [51,52].

The exact pathogenic of DIM is poorly understood [51-53], some of cases are noted in patients with connective tissue diseases, autoimmune diseases or vasculitis[49,52,53,61,76,78,81,82] suggesting a possible predisposing immune dysregulation[53].

This hypothesis is supported by an abnormal upregulation of interleukin 6 in both cerebrospinal fluid and plasma associated with this type of meningitis [53,83-87]. Magnetic resonance imaging showed that DIM can be also associated with signal abnormalities of cerebrospinal white-matter that resolved several days after discontinuing the incriminated agent [49,52,83].

Hypersensitivity type I or III and cytokine release (mainly or exclusively limited to the CSF compartment) are possible mechanisms invoked in DIM pathogenesis [52,88]. For other authors, direct meningeal drug-toxicity/irritation is also evocated as a possible pathogenic mechanism of DIM [52,88].

Recurrent DIM was also reported (2 to 5 episodes in the same patient), especially with non-steroid anti-inflammatory drugs [89,90], antibiotics [91], OKT3 [86], and intravenous immunoglobulin [92]. Systemic diseases (systemic lupus erythematosus, Sjogren’s syndrome, undifferentiated connective tissue disease, and rheumatoid arthritis), idiopathic thrombocytopenic purpura, human immunodeficiency virus infection, and Crohn’s disease are the most frequent conditions associated with recurrent DIM [92,97].

Others exceptional causes

Exceptional causes can be also listed for NIM : fested-branch angitis [98], chronic urticaria [99], Fabry disease with ischemic stroke [100], posterior fossa dermoid cyst [101], intracranial epidermoid cyst [102,103], spontaneous rupture of spinal teratoma [104], trans-sphenoidal management of Rathke’s dect cyst [105], glyphosate-surfactant herbicide poisoning [106], acute disseminated encephalomyelitis [107], SAPHO syndrome [108], brain surgery [109], metal fume fever complication of Zinc oxide fume inhalation [110], reaction to intracranial infections (brain or sinus) [111,112], scinti-ysternography with [111] indium-DTPA [113], and microdiscectomy [114].
Management of aseptic meningitis

The diagnosis of non-infectious aseptic meningitis is a real challenge for the clinician. Indeed, in most cases, neither clinical presentation nor cerebrospinal fluid characteristics are discriminative for etiologic diagnosis.

When we have aseptic meningitis, we have first to eliminate viral causes because they are responsible for the majority of these meningitis. The main causal viruses are: enteroviruses, Herpes Simplex Virus, Varicella Zoster Virus, West Nile Virus, Human Immunodeficiency Virus, mumps. Specific serological tests and PCR have a great contribution in these situations.

Subsequently, it is necessary to perform specific tests looking for bacterial or fungal causes that can lead to aseptic meningitis, mainly: tuberculosis, syphilis, brucellosis, Lyme disease, Cryptococcus neoformans.

When we have aseptic meningitis caused by herpes simplex virus (principally HSV-2 and less frequently HSV-1), remains a main differential diagnoses for aseptic meningitis.

Finally, the diagnosis of non-infectious aseptic meningitis is based on a set of arguments: clinical, biological, immunological, and radiological:

- A complete and repetitive physical examination is necessary to look for signs of systemic involvement suggestive of system disease, granulomatosis or systemic vasculitis: rash, purpura, mucosal ulcers, aphthous ulceration, genital ulcers or scars, arthritis, synovitis, peripheral neuropathy, uveitis, pleurisy, pericarditis.

- The search for signs evoking cancer or hematologic malignancies such hepatomegaly, splenomegaly, lymphadenopathy or other organomegaly.

- Antecedent for atopy or allergy and the history of recent drug intake are important to clarify, especially for the diagnosis of DIM.

- Specific additional tests will be required depending on the diagnostic orientation: screening of autoantibodies (antinuclear antibodies, antibodies to native DNA, antibodies to soluble antigens, ANCA (antineutrophil cytoplasmic antibodies c and p), and organ-specific autoantibodies), tumor markers, radiological investigations (ultrasound, CT-scans, MRI), bone marrow aspirate, bone marrow biopsy, genetic tests, endoscopic explorations, organ biopsies.

- Diagnosis of DIM must remain a diagnosis of exclusion after removing infectious, neoplastic and inflammatory causes. It is based on the notion of recent drug use, the temporal relationship between drug intake and onset of meningeal signs, negativity of cerebrospinal fluid (direct examination and cultures), and the resolution of meningeal symptoms after drug withdrawal.

CONCLUSION

Aseptic noninfective meningitis are uncommon but represent a veritable diagnostic challenge to the clinician because their clinical and cerebrospinal fluid profile are similar to those of infectious meningitis.

Their diagnosis rests on clinical symptoms of meningitis, typical biological findings in the CSF, negativity of the infectious tests (bacterial, viral, parasitic and fungal), and a personal history of subjacent diseases (connectivities, autoimmunity, cancers, granulomatosis, vasculitides), drug catches, brain surgery or neurological invasive explorations.

Multiple causes can be listed and usually classified in three main groups: systemic diseases with meningeal involvement, neoplastic meningitis, and drug-induced aseptic meningitis. However, it should be noted that in about 30% of the cases, no cause is identified in spite of an extensive etiologic investigation; thus it is called "idiopathic meningitis" which is generally chronic and/or recurring.

REFERENCES

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