A Differential Diagnosis of Drug-Induced Aseptic Meningitis

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Drug-induced aseptic meningitis should be included in the differential diagnosis of viral/aseptic meningitis. Clinicians should use historical clues in patients presenting with signs and symptoms of viral meningitis to aid in the differentiation of drug-induced aseptic meningitis from other causes of aseptic meningitis. Viruses are the most common cause of aseptic meningitis, with enteroviruses being the most common among viruses in cases presenting as aseptic meningitis. Ibuprofen is currently the most common cause of drug-induced aseptic meningitis. Drug-induced aseptic meningitis is a benign condition without long-term sequelae. The diagnosis of drug-induced aseptic meningitis is made by establishing a causal relationship between the use of the drug and the onset of signs and symptoms, supported by negative tests for infectious causes of symptoms and rapidity of resolution after the drug is discontinued. [*Infect Med.* 2008;25:331-334]

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Aseptic meningitis refers to a nonbacterial inflammation of the leptomeninges.[1] Viruses are the most common cause of aseptic meningitis, and the most common viruses that cause aseptic meningitis are enteroviruses. Drug-induced aseptic meningitis is rare but probably more common than the literature would suggest; therefore, it should be included in the differential diagnosis of aseptic meningitis, particularly if aseptic meningitis develops in association with the use of NSAIDs or other offending drugs (Table 1) and if clinical recovery is rapid following cessation of the drug or if results of viral studies are negative.

The pathogenetic mechanisms of drug-induced aseptic meningitis are not fully understood, but 2 major mechanisms have been proposed. One proposed mechanism is that the meninges are directly irritated by the intrathecal administration of drugs. The other is that the meninges are expressing an immunological hypersensitivity—most often a type 3 or type 4 hypersensitivity reaction—to the offending drug.[2]

An association between hypersensitivity reactions and underlying collagen-vascular disease or rheumatological disease has been reported.[1-10] Typically, the cerebrospinal fluid (CSF) profile in drug-induced aseptic meningitis is that of a neutrophilic pleocytosis accompanied by a normal CSF lactic acid level and a variably elevated CSF protein level.[1,3] Patients who have drug-induced meningitis may have eosinophils present in the CSF (fewer than 5%).

THE CLINICAL PICTURE

Patients who have drug-induced aseptic meningitis typically present with fever, headache, and nuchal rigidity. Signs and symptoms usually appear within 24 to 48 hours after drug ingestion, but symptoms may not occur until 2 years post-therapy.[2,6] Drug-induced aseptic meningitis may develop in a patient who initially was able to tolerate the causative drug.[1,6]

In patients who have drug-induced aseptic meningitis, the typical CSF profile reveals a neutrophilic pleocytosis, with several hundred to several thousand white blood cells

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Table 1 – Medications known to cause aseptic meningitis

Medications	Common	Uncommon	Rare
NSAIDs	Ibuprofen	Sulindac Naproxen Diclofenac Rofecoxib	Ketoprofen Salicylates[a] Tolmetin Piroxicam Celecoxib
Antimicrobials	Trimethoprim/ sulfamethoxazole Trimethoprim	Sulfonamides	Cephalosporins Penicillin Amoxicillin Amoxicillin/clavulanate Isoniazid Ciprofloxacin Metronidazole Pyrazinamide Valacyclovir Indinavir Ornidazole
Immunomodulating agents	Monoclonal antibody OKT3 Intravenous IgG	Azathioprine	Levamisole Efalizumab Infliximab Sulfasalazine
Intrathecal agents		Metrizamide Cytarabine Methylprednisolone acetate	Methotrexate Gentamicin Iophendylate Iopamidol Iohexol Hydrocortisone Baclofen Gadolinium Diethylenediamine pentaacetic acid Spinal anesthesia
Other		Carbamazepine	Monovalent mumps and rubella vaccine Hepatitis B vaccine Ranitidine Famotidine Dexchlorpheniramine Phenazopyridine Radiolabeled albumin Lamotrigine Allopurinol Pentoxifylline Methotrexate

[a] With serum levels ≈ 70 mg/dL.

Adapted from Hopkins S, Jolles S. *Expert Opin Drug Saf*. 2005[3]; Marinac J. *Ann Pharmacother*. 1992.[4]

per microliter; normal glucose levels; and variably elevated protein levels.[1,2,4-7] Results of CSF Gram stain and cultures are negative, and lymphocytic or eosinophilic pleocytosis may occur. Drug-induced aseptic meningitis is reversible, with most signs and symptoms resolving within 24 to 48 hours after the drug is discontinued.[2,4-7]

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of aseptic meningitis is extensive and includes infectious and noninfectious causes (Table 2).[1-10] Drug-induced aseptic

Table 2 – Causes of acute aseptic meningitis

	Common	Uncommon	Rare
Infectious causes			
Bacterial	Lyme disease Leptospirosis *Mycobacterium tuberculosis* infection Subacute bacterial endocarditis Parameningeal infection (epidural subdural abscess, sinus or ear infection) Partially treated bacterial meningitis	*Treponema pallidum* infection *Mycoplasma pneumoniae* infection Rocky Mountain spotted fever Brucellosis Ehrlichiosis	*Borrelia recurrentis* infection (relapsing fever) *Spirillum minus* infection (rat-bite fever) Nocardiosis *Actinomyces* infection
Viral	Echovirus infection Coxsackievirus infection Mumps St Louis encephalitis Eastern equine encephalitis Western equine encephalitis California encephalitis Herpes simplex virus type 1 infection Herpes simplex virus type 2 infection HIV infection Lymphocytic choriomeningitis Poliovirus infection	Epstein-Barr virus infection Adenovirus infection Cytomegalovirus infection Varicella Measles Rubella	Parainfluenza virus infection Rotavirus infection Vaccinia virus infection West Nile virus infection Human herpesvirus 6 infection Japanese B encephalitis Murray Valley encephalitis
Fungal		Cryptococcosis Coccidioidomycosis Histoplasmosis	Candidiasis Blastomycosis Aspergillosis Sporotrichosis
Parasitic		*Angiostrongylus cantonensis* infection Toxoplasmosis	Cysticercosis *Trichinella spiralis* infection
Noninfectious causes			
Neoplastic diseases	Intracranial tumors Lymphoma Leukemia Metastatic carcinomas		
Systemic diseases		Neurosarcoidosis Behçet disease Systemic lupus erythematosus	Vogt-Koyanagi-Harada syndrome Sjögren syndrome Rheumatoid arthritis
Neurosurgical procedures		Neurosurgery (posterior fossa syndrome) Intrathecal agents	
Medications	See Table 1		

Adapted from Chaudhry HJ, Cunha BA. *Postgrad Med.* 1991[1]; Connolly KJ, Hammer SM. *Infect Dis Clin North Am.* 1990.[8]

meningitis is a diagnosis of exclusion. It is important to obtain a history of medical disorders such as systemic lupus erythematosus, the most frequent underlying condition associated with drug-induced aseptic meningitis.[7] It is also important to make inquiries about recent vaccinations that may be implicated in the development of aseptic meningitis.[2]

Patients with enteroviral meningitis often present with an early neutrophilic pleocytosis, although a shift to lymphocytic pleocytosis usually occurs within the first 48 hours.[1,4,7,10] In normal hosts, enteroviral meningitis has a benign course, usually lasting about 2 weeks. Recovery is typically characterized by decreasing frequency of headaches and stiff neck within the 2-week period.[7,9] The condition may be diagnosed by polymerase chain reaction testing of the CSF, by viral culture of throat and rectal specimens, or by serological tests for enteroviruses. CSF lactic acid levels readily differentiate bacterial from viral meningitis.[9]

Quick resolution of symptoms is an important sign that distinguishes drug-induced aseptic meningitis from viral meningitis, in which recovery usually requires 10 to 14 days.[7] CSF glucose levels are usually normal in drug-induced aseptic meningitis, which may help in differentiating it from bacterial meningitis in which glucose levels usually are low.[4,6,7,10]

Analysis of C-reactive protein (CRP) levels also may be helpful in distinguishing bacterial from a drug-induced aseptic meningitis because CRP levels are usually highly elevated in bacterial meningitis compared with drug-induced aseptic meningitis.[2,5] The diagnosis of drug-induced aseptic meningitis is made by establishing a temporal relationship with the administration of the drug and onset of clinical symptoms and rapid resolution of the syndrome after drug withdrawal.[2-4,7,10]

The most common cause of drug-induced aseptic meningitis is NSAIDs. The list of medications that cause drug-induced aseptic meningitis continues to increase and currently includes a wide variety of medications (Table 1).[11-28]

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