REVIEW ARTICLE

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Drug-Induced Aseptic Meningitis
Diagnosis and Management

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Abstract

Drug-induced aseptic meningitis (DIAM) has been reported as an uncommon adverse reaction with numerous agents. It is a diagnosis of exclusion, and clinical signs and CSF findings vary greatly. The body of evidence regarding DIAM is largely in the form of anecdotal case reports and must be interpreted carefully bearing this in mind.

The major categories of causative agents are nonsteroidal anti-inflammatory drugs, antimicrobials, intravenous immunoglobulin, intrathecal agents, vaccines and a number of other less frequently reported agents. There appears to be an association between DIAM and connective tissue disease, particularly systemic lupus erythematosus, and ibuprofen.

There are 2 major proposed mechanisms for DIAM. The first involves direct irritation of the meninges by intrathecal administration of the drug, and the second involves immunological hypersensitivity to the drug, most likely type III and type IV hypersensitivity.

Recognition and diagnosis of DIAM is important, as it is treatable by withdrawal of the drug and recurrence is prevented. The outcome of DIAM is generally good, usually without long term sequelae.

This article describes the case reports of DIAM in the current literature and discusses the diagnosis and management of this rare complication.

This review aims to define drug-induced aseptic meningitis (DIAM) and to discuss the classes of causative agents, their potential mechanisms of action, predisposing factors to DIAM and its management. A literature search (1966 to 2000) has been used to identify background literature and all published reports of DIAM using Medline, Science Citation Index and Drugdex (Micromedex) Adverse Reactions Index.

Meningitis is defined as inflammation of the brain and spinal cord membranes (meninges) and is distinct from encephalitis, which is an inflammation of the brain tissue. The causes of meningitis are either infective (bacterial, viral, fungal or protozoal) or noninfective. The noninfective (aseptic) causes include drugs, primary tumours of the central nervous system (CNS), carcinomas, granulomatous angiitis, sarcoidosis, systemic lupus erythematosus (SLE), rheumatoid arthritis, Behçet's syndrome, Vogt-Koyanagi-Harada syndrome and Mollaret's meningitis.[1-3] Historically, aseptic meningitis included forms of infective meningitis (viral and fungal) that were negative on Gram stain. However, with the introduction of improved laboratory techniques and polymerase chain reaction (PCR)–based investigations, sensitivity has increased and a larger proportion of cases are now diagnosed as viral meningitis.

The clinical features of acute meningitis include fever, headache, photophobia, neck stiffness, nausea, vomiting, arthralgia, myalgia, rash and abdominal pain. The type of meningitis cannot be ascertained by presenting symptoms and signs alone, and CSF analysis for protein, glucose, differential white cell count and organisms, in addition to other specialised investigations, guide diagnosis and management. CSF findings in DIAM vary considerably; however, there is usually a pleocytosis of a hundred to several thousand cells per microlitre. Although polymorphonuclear predominance is most common, lymphocytic and eosinophilic findings are also reported. CSF protein levels are usually elevated, whereas glucose is normal. By definition, CSF culture results are negative.

DIAM is a diagnosis of exclusion and depends on the establishment of a causal relationship with the drug concerned, taking into account timing of administration, clinical features, compatible CSF findings and confirmation by rechallenge. Analysis of the DIAM literature is complicated by incomplete evidence in many reports, with the diagnosis of DIAM based solely on clinical signs and symptoms with no objective evidence, CSF analysis or rechallenge to prove the presence of aseptic meningitis or confirm the relationship to the drug.

1. Drugs Causing Aseptic Meningitis

Many drugs have been implicated as causes of aseptic meningitis. These fall into a number of major categories: nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials, intravenous immunoglobulin, intrathecal agents, vaccines and miscellaneous drugs.

1.1 Nonsteroidal Anti-Inflammatory Drugs

NSAIDs constitute the largest category of reports of DIAM.[4] Eight NSAIDs have been implicated (tables I and II), with ibuprofen by far the most common cause of DIAM. DIAM is still a rare adverse effect, not related to class of NSAID or prostaglandin inhibition, as most patients may be successfully treated with an alternative NSAID without incident. However, there are cases where patients have experienced DIAM with several NSAIDs.[35,48] DIAM usually begins rapidly after administration, but has been reported to occur up to 2 years into treatment.[36] Patients with SLE and connective tissue disease appear to be predisposed to DIAM associated with NSAIDs, with ibuprofen again the most frequently cited drug.[20] A few reports of aseptic meningitis in previously healthy patients have also been published.[15]

Small doses of ibuprofen have caused DIAM, for example after over-the-counter purchase of the drug,[21] after only the third 200mg tablet[14] or even after a single 400mg dose.[22] Aseptic meningitis with iridocyclitis has also been attributed to ibuprofen.[23] In addition to the more common signs and symptoms of aseptic meningitis, numer-

ous other, less frequent, clinical features reported include lethargy, seizures, confusion (particularly in the elderly), periorbital oedema, diplopia, conjunctivitis, hypotension, parotitis, pancreatitis, liver function test abnormalities, pruritus and pericarditis.

Table I. Ibuprofen-induced aseptic meningitis. Each line represents a separate patient. Some patients were rechallenged with the drug; the number of positive rechallenges reported is shown

Associated disease	No. of positive rechallenges in this patient	Reference
ANA, RF	1	26
Connective tissue disease	1	17
	2	5
	ND	5
	ND	25
Osteoarthritis	1	28
	ND	16
Polyarthritis	ND	29
Rheumatoid arthritis	1	7
	1	12
SLE	1	11
	1	14
	1	18
	1	18
	1	19
	1	20
	1	32
	ND	6
	ND	8
	ND	9
	ND	13
	ND	18
	ND	21
	ND	27
	ND	29
	ND	30
	ND	33
	ND	35
None	1	32
	3	31
	ND	10
	ND	15
	ND	23
	ND	22
	ND	29
	ND	24
	ND	29
	ND	34
	ND	35

ANA = antinuclear antibody positive; **ND** = not done; **RF** = rheumatoid factor positive; **SLE** = systemic lupus erythmatosus.

Five cases of sulindac-induced aseptic meningitis have been reported. One patient had SLE[39] and 2 had mixed connective tissue disease;[43] the other 2 patients had no evidence of connective tissue disease,[42] 1 developing DIAM despite asymptomatic exposure to numerous other NSAIDs.[41]

Naproxen has been implicated as causing DIAM in 3 patients. One was a male being treated for neck spasms who developed signs, symptoms and CSF findings of aseptic meningitis 1 week after starting the drug.[37] The second was a female with SLE who developed 3 episodes of aseptic meningitis after 2 years of intermittent naproxen intake before a temporal connection with the drug was recognised.[36] The third patient had 7 episodes of DIAM with naproxen, diclofenac, or piroxicam being prescribed in the 3 months prior to the last 4 episodes.[38]

Tolmetin was reported as a causative agent of DIAM in a female patient with SLE who had previously experienced DIAM associated with ibuprofen. In addition to meningitis, she experienced drug-induced hepatitis and painful cervical lymphadenopathy.[48]

Diclofenac, alone[46] and associated with SLE,[47] along with ketoprofen[44] and piroxicam,[38] are rarer causes of aseptic meningitis. Salicylate-induced DIAM has been reported only in the context of overdose.[45]

1.2 Antimicrobials

The reporting of antimicrobial-associated DIAM is complicated by previous antimicrobial therapy, since patients may receive several different agents in the treatment of an infection. Careful interpretation of data is also required, as prior antimicrobial treatment may result in culture-negative CSF in partially treated bacterial meningitis.

Cotrimoxazole (trimethoprim-sulfamethoxazole) is the antimicrobial most frequently associated with aseptic meningitis, and 26 cases have been reported (table III). Of these patients, 3 were HIV positive, 2 had SLE, 2 had Sjögren's syndrome, 1

Table II. Aseptic meningitis induced by nonsteroidal anti-inflammatory drugs other than ibuprofen

Drug	Onset	Associated disease	Reference
Naproxen	Onset varies from 1wk after 2nd course to as long as 2y into course	May be associated with SLE	36, 37, 38
Sulindac	1h after drug (2nd course)	Lower incidence than ibuprofen	39, 40, 41, 42, 43
		May be associated with SLE	
		Also reports in absence of underlying systemic rheumatic disease	
Ketoprofen			44
Salicylates		After overdose	45
Diclofenac	2wk	May be associated with SLE	46
		Also reported in patients with rheumatic disease	38, 47
Tolmetin		With SLE	48
Piroxicam		No connective tissue disease	38

SLE = systemic lupus erythematosus.

was antinuclear antibody positive and 1 had Crohn's disease; the remainder had no disease association. The association with autoimmune disease is still evident, although not as strong as with NSAIDs[56,59,60] (reviewed by Joffe et al.[51]).

Trimethoprim alone may also cause DIAM[53,61] and has been described in association with uveitis.[68] Cephalosporins have been implicated in a woman who had several episodes of aseptic meningitis associated with exposure to cefalexin, cefazolin and ceftazidime.[74] She was shown to have specific IgG to ceftazidime, and skin prick testing with cefazolin provoked a recurrence of meningitis. Penicillin has been reported as causing meningitis in a woman after parenteral administration. This resulted in headache with raised intracranial pressure, vertigo, tinnitus, fever, mild deafness and scleritis.[73] Isoniazid used as monotherapy prophylaxis for a positive Mantoux test has been reported in a healthy man as causing DIAM which recurred on rechallenge.[72] Oral ciprofloxacin has resulted in an eosinophilic meningitis with 24% eosinophils, 76% mononuclear cells, mildly elevated protein and normal glucose.[71] Metronidazole has also been reported as a cause of DIAM.[75] Gentamicin was reported as a cause of meningeal inflammation following bacterial meningitis,[76] but in this case the antimicrobial was administered intrathecally.

1.3 Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is a recognised cause of aseptic meningitis;[77-96] however, there is a spectrum of symptoms ranging from acute headache[85] to frank aseptic meningitis.[78,82,86,97] IVIG is a plasma product, made from the pooled plasma of 10 000 to 20 000 healthy donors. It contains immunologically active molecules (interferon-γ, transforming growth factor-β and soluble CD4) in addition to a range of stabilisers that vary according to the product concerned. DIAM tends to occur within 48 hours of the infusion but may occur later, and is much less frequent in patients receiving replacement doses of IVIG (200 to 400 mg/kg) every 2 to 3 weeks than in patients treated with high dose IVIG (2 g/kg/month). There is no clear relationship with a particular IVIG product, and changing the preparation is not usually successful in preventing the condition.

There have been various estimates of the incidence of aseptic meningitis. In a study of 54 patients receiving high dose IVIG for immune neuromuscular disease, 6 developed aseptic meningitis confirmed by CSF analysis.[77] In a further study of high dose IVIG used to treat 83 patients with idiopathic thrombocytopenic purpura, 3 patients reported severe headache but none had formally demonstrated aseptic meningitis.[98] Aseptic meningitis related to high dose IVIG appears more fre-

quently in the literature than other adverse effects, such as haemolytic anaemia or renal failure. Patients with pre-existing migraine receiving high dose IVIG have been suggested to be at higher risk of developing aseptic meningitis.[77]

A number of measures are helpful in preventing or reducing the problems associated with high dose IVIG.[99] The initial infusion should be given at a slow rate (not faster than 6 g/h) and at a 3% dilution. If this infusion is uncomplicated the rate and concentration may be increased. Prehydration is important and patients are encouraged to maintain a good fluid intake throughout treatment. Paracetamol (acetaminophen) alone or with codeine is used as premedication and in some cases antihistamines (cetirizine) have been of benefit. A number of reports of aseptic meningitis describe eosinophils in the CSF, and cetirizine may have effects on their migration in addition to H_1 blockade.[99,100] The symptoms of aseptic meningitis are not always recurrent and treatment can often be continued if appropriate action is taken. In our experience, corticosteroids have not been of great benefit in the management of high dose IVIG-induced aseptic meningitis, and symptoms may occur even when patients are receiving high dosages of corticosteroids prior to the introduction of high dose IVIG. Recognition of aseptic meningitis when using high dose IVIG is important to allow intervention and continuation of therapy.

1.4 Intrathecal Agents

The introduction of a drug into the CSF may result in direct meningeal irritation and the clinical findings of aseptic meningitis. These findings can be delayed by up to several weeks after administration of the drug. The toxicity or likelihood of irritation is related to concentration, lipid solubility, particle size, ionic strength and duration of contact with the CSF. Interpretation of the case reports of intrathecal agents and DIAM should take into account any existing CNS disease and the injection of substances other than the suspected drug such as anaesthetic, diluent and contaminants.

Table III. Antimicrobial-induced aseptic meningitis. Each line represents a separate patient. Some patients were rechallenged with the drug; the number of positive rechallenges reported is shown

Drug	Associated disease	No. of positive rechallenges in this patient	Reference
TMP-SMX or trimethoprim	ANA	1	52, 53
	CD	2	62
	HIV	1	65
	HIV	2	69, 70
	HIV	ND	54
	HIV	ND	52, 53
	RA	4	60
	SLE	1	52, 53
	SLE	2	63
	SS	1	52, 53
	SS	5	58
	SS	ND	68
	None	1	51
	None	1	55
	None	1	59
	None	1	61
	None	1	61
	None	1	52, 53
	None	1	52, 53
	None	2	64
	None	3	30
	None	4	66
	None	ND	49
	None	ND	50
	None	ND	54
	None	ND	56
	None	ND	57
	None	ND	61
	None	ND	67
Cephalosporins	None	Several	74
Ciprofloxacin	None	0	71
Isoniazid	None	1	72
Metronidazole	None	1	75
Penicillin	None	0	73
Sulfamethoxazole	None	0	57

ANA = antinuclear antibody positive; **CD** = Crohn's disease; **HIV** = human immunodeficiency virus; **ND** = not done; **RA** = rheumatoid arthritis; **SLE** = systemic lupus erythematosus; **SS** = Sjögren's syndrome; **TMP-SMX** = cotrimoxazole (trimethoprim-sufamethoxazole).

There are numerous reports of both oil- and water-soluble radiographic contrast media precipitating aseptic meningitis, usually following myelography.[52,101-108] Clinical findings (fever, headache

and photophobia) may appear within hours of the procedure or be delayed by over 2 weeks. CSF analysis usually shows lymphocytosis and elevated protein with reduced glucose; eosinophilia has also been reported.[101,102]

An early report of DIAM followed the injection of ^{111}indium-diethylenetriaminetetra-acetic acid for cysternography.[109] Similar reports have been made for metrizamide in both adults[103] and children.[105] In some cases the symptoms also included Guillain-Barré syndrome[110] or worsening of SLE.[107] Lophendylate[102] and iopamidol (in dogs)[111] have also been implicated. The magnetic resonance imaging contrast agent gadolinium diethylenediaminepenta-acetic acid has been the subject of a single case report.[112]

Both methylprednisolone acetate[113-116] and hydrocortisone sodium succinate[117] have been described as a cause of aseptic meningitis following intrathecal administration. Chemotherapeutic agents such as methotrexate and cytarabine may cause aseptic meningitis. Intrathecal methotrexate was used in the treatment of a 4-year-old boy with acute lymphoblastic leukaemia, and, once recovered from the aseptic meningitis, he completed his treatment with oral methotrexate without incident, which argues against an immunologically mediated mechanism.[118] Systemic and intrathecal cytarabine may cause both aseptic meningitis and cerebellar dysfunction.[108,119-125]

The intrathecal administration of baclofen[126] has been described as a cause of aseptic meningitis.

Spinal anaesthesia has also been associated with aseptic meningitis, and contaminants within the preparation injected, such as phenolic disinfectant,[127] detergent[128] and starch from surgical gloves,[129] have been implicated.

1.5 Vaccines

Aseptic meningitis is a rare but well recognised complication of certain vaccines, and a history of recent vaccination should be sought when assessing a patient with possible DIAM. Vaccines associated with aseptic meningitis include measles, mumps and rubella[130] and monovalent mumps and rubella.[131-133] Nucleotide sequences of the mumps virus have been isolated from the CSF in cases of aseptic meningitis.[134] Theff identification of an infective agent in the CSF (albeit vaccine strain mumps) means that these reactions do not fall into the definition of DIAM and would be more correctly termed viral meningitis. Of interest, the incidence of wild mumps–associated meningitis was 4-fold higher than vaccine-associated mumps meningitis, although different vaccine strains cause varying incidences of viral meningitis.

An alternative mechanism relating to an immune response to the vaccine is operative when the vaccine is a killed preparation or component vaccine. The diphtheria, tetanus and pertussis (DTP) vaccine, although associated with acute encephalopathy in children, has not been associated with frank aseptic meningitis.[135] Aseptic meningitis following immunisation against hepatitis B vaccine has been reported.[136]

1.6 Miscellaneous Drugs

Carbamazepine has been associated with aseptic meningitis in 4 case reports.[137-140] Only one of these was associated with connective tissue disease (Sjögren's syndrome), and to our knowledge there are no reports with newer anticonvulsants.

Monoclonal antibodies against CD3 (anti–T cell antibodies) causing aseptic meningitis have been the subject of many case reports.[141-151] The estimated incidence of this adverse effect is approximately 2%. Occurrence is within 24 to 72 hours and tends to last up to 5 days. CSF analysis reveals a neutrophilic predominance with elevated protein and normal glucose. This may be part of the cytokine release syndrome that can accompany administration of anti-CD3 monoclonal antibodies.[152]

Azathioprine has been reported to cause DIAM in 4 patients with SLE, some of whom were also treated with prednisolone; however, 2 patients had an episode of meningeal symptoms with azathioprine alone.[153]

Several HIV-positive patients in a study using indinavir[154] were reported to have had aseptic meningitis. It should be remembered that primary

HIV infection may result in CNS symptoms and that highly active antiretroviral therapy (HAART) might result in increased immunopathology as T cell recovery occurs. Abnormal liver function tests have been observed in patients coinfected with HIV and hepatitis C who received HAART, as a degree of T cell reconstitution allows renewed attack on the hepatitis C virus.

Other drugs associated with rare episodes of DIAM include ranitidine,[155] sulfasalazine,[156,157] phenazopyridine,[158] pyrazinamide,[159] levamisole and radiolabelled albumin.[160]

2. Mechanisms

The mechanisms believed to underlie DIAM are divided into 2 main categories. The first is a direct chemical 'irritation' of the meninges (attributed to differences in lipid solubility, ionic strength, particle size and pH) by drugs introduced into the CSF, e.g. contrast media such as metrizamide and iophenylate as well as baclofen, anaesthetics, methylprednisolone, hydrocortisone and contaminants. The second proposed mechanism is an immunological hypersensitivity reaction that may be further subdivided into type I to type IV hypersensitivity.

Type I is the classical allergic IgE-mediated reaction associated with release of mast cell and basophil inflammatory mediators following binding of the antigen to specific IgE bound to mast cells, basophils or eosinophils. This can be tested for by using skin prick tests or assays of specific IgE by radioallergosorbent testing (RAST). This type of reaction would be of rapid onset and accompanied by urticaria, wheezing, fall in blood pressure and other symptoms of an allergic reaction; these are not often observed in the setting of DIAM.

Type II hypersensitivity occurs when antibodies bind to a cellular target and complement is activated. This would happen only if the drug or a breakdown product were displayed on the cell surface and if the cell was localised in the meninges.

Types III and IV hypersensitivity are more likely mechanisms. In these reactions, antibodies combine to form complexes with the drug (or a metabolite) in the serum, activating complement (type III), or T cells reactive to the drug are recruited to a site of inflammation (delayed type hypersensitivity or type IV). Type III hypersensitivity is a plausible mechanism, particularly in the setting of SLE, which is believed to represent an immune complex-mediated disease, and in HIV infection where a dysregulated hypergammaglobulinaemia exists. Support for this mechanism would be the demonstration of specific IgG antibodies to the drug or its metabolites and the demonstration of immune complexes in the CSF. Up to 60% of patients with SLE are estimated to have CNS symptoms associated with inflammation at some stage of their disease and this may predispose them to DIAM. The autoantibody profiles of patients with SLE and DIAM have not been studied in detail; however, the number of reports linking connective tissue disease, and in particular SLE, with DIAM (especially with ibuprofen) is striking, particularly when compared with the vast number of patients taking aspirin (acetylsalicylic acid) for cardiovascular indications in whom DIAM has yet to be reported. It is also interesting to note that there are no reports of DIAM in drug-induced SLE. Some NSAIDs also have effects on leucocyte migration,[161] and it may be that alterations in adhesion molecules play a role in directing these cells to the CNS, resulting in DIAM.

Type IV hypersensitivity involves T helper cells and takes place over 24 to 48 hours after previous sensitisation, requiring presentation of peptides to the T cells by antigen-presenting cells such as macrophages, dendritic cells and, in the brain, microglial cells. This mechanism is invoked in contact sensitivity where patch testing is used in diagnosis. In DIAM, however, there may be little role for a test which assesses the antigenic specificity of skin-homing lymphocytes. The cellular nature of this reaction means that it is more readily treatable with corticosteroids; however, these are not usually effective in DIAM. The time course of DIAM and cellular changes observed in the CSF could implicate type IV hypersensitivity as a mechanism. The release of cytokines and other mediators of inflam-

mation may have an effect on endothelial integrity, particularly that of the blood-brain barrier. This may be of particular relevance in DIAM secondary to administration of anti-CD3 monoclonal antibody.

There may be multiple mechanisms operating in DIAM, and it is important to note the rate of onset of symptoms and their resolution as well as using the tests available (skin prick tests, assays for specific IgG against drugs or metabolites, and patch testing) where clinically appropriate, to further define the pathogenesis and allow more rational treatment.

Further research is needed to better define the pathogenesis of DIAM. Immunologists should be more involved in investigating this rare adverse event, in which immunological mechanisms are believed to play a major role.

3. Management

DIAM is a diagnosis of exclusion and it is vital that infection is excluded in a patient presenting with meningeal signs and symptoms (fever, headache, nausea, vomiting, neck stiffness). This is particularly important in patients who have recently taken antimicrobials and who may have a partially treated bacterial meningitis. A careful history is needed to establish underlying diseases that may manifest with an aseptic meningitis presentation, recent vaccination or exposure to other causative agents, recent lumbar puncture, or viral infections. A note should be made of all medications taken and their relationship to the onset of symptoms, previous reactions to the suspected agent or similar drugs, and recurrence of symptoms with rechallenge. Predisposing factors such as connective tissue disease (especially SLE) and migraine should be sought. It is useful to check inflammatory markers such as C-reactive protein, as this would be very high in bacterial infection and less so in inflammation due to other causes. MRI scanning may reveal meningeal enhancement in DIAM.

When DIAM is suspected, the drug should if possible be discontinued, and any infection risk should be promptly covered with appropriate antimicrobial, such as a third generation cephalosporin,[162] until a negative CSF infection screen is confirmed. Symptoms of pruritus and nausea may be treated with antihistamines and antiemetics in addition to analgesics for the headache. In the case of high dose IVIG, fluid intake should be encouraged and intravenous saline may hasten the resolution of headache if this is already established. If further high dose IVIG treatments are required, premedication with a combination of antihistamines, paracetamol and hydration, and a slow IVIG infusion rate, may prevent or lessen symptoms.

If doubt exists about the diagnosis of DIAM it may be confirmed by supervised rechallenge. The issue of rechallenge to enable a drug to be continued, if it is deemed vital, or if the diagnosis of DIAM is essential, is problematic, as no evidence-based rechallenge protocol exists. The aim of rechallenge, in the first instance, is to ascertain tolerance to the drug at therapeutic dosages and thus any protocol should utilise a dosage at the lower end of the treatment dosage range. In the second instance, testing is for sensitivity to the drug, and the risk-benefit ratio must be carefully assessed in each case. Informed consent should be sought from the patient, and the rechallenge must be medically supervised both to document the response and to offer medical care and advice if required. The duration of supervision will vary depending on the individual case and the timing of the previous reaction(s).

4. Conclusion

DIAM has been reported as an uncommon adverse reaction with numerous drugs and chemicals and should be considered in the differential diagnosis of acute and recurrent meningitis. The major categories of causative agents are NSAIDs, antimicrobials, IVIG, intrathecal agents and vaccines, with a number of other agents reported less frequently. The association between SLE and ibuprofen as cause of DIAM is particularly strong and is important to recognise, as this medication may be purchased over the counter. DIAM is treatable by withdrawal of the drug and does not usually

result in long term sequelae, even where repeated exposure to the drug has occurred.

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