

A number of cases in the Global survey had a history of one or more episodes of chemical meningitis preceding their arachnoiditis.

Some authors in fact refer to episodes as chemical arachnoiditis.

Jolles et al. at the National Institute for Medical Research, London, ([\[1\]](#)) discussed Drug-induced aseptic meningitis (DIAM), which they denoted as "uncommon."

The authors remarked that most of the literature comprises anecdotal case reports.

The major types of causative drugs are nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials (antibiotics)

"intravenous immunoglobulin, intrathecal agents, vaccines".

The authors also noted the association between lupus and DIAM and the link with ibuprofen.

They stated that up to 60% of patients with SLE are estimated to have CNS symptoms associated with inflammation at some time during their illness, and that this could predispose them to DIAM.

They postulated 2 possible ways in which DIAM arises:

1. Direct irritation of the meninges by intrathecal administration of the drug, and
2. Immunological hypersensitivity to the drug.

In regard to intrathecally-administered drugs, Jolles noted that direct meningeal irritation might manifest itself several weeks after administration of the drug.

Toxicity is related to concentration, lipid solubility, particle size, ability to ionise the CSF and duration of contact with CSF.

Notably, Jolles remarks on the need to consider injection of substances other than the suspected drug, such as anaesthetic, diluent or contaminant. To that I would also add preservatives, as already discussed.

The paper goes on to note the numerous reports relating to myelography contrast media, both oil and water-soluble, precipitating acute meningitis ([\[2\]](#) ; [\[3\]](#)).

This may cause clinical symptoms within hours or delayed by as much as 2 weeks.

Cases of chemical meningitis due to myelography dyes were reported by various authors. Vik-Mo and Maurer ([\[4\]](#)) in 1975 suggested that severe acute meningeal reactions after lumbar myelography could be due to contamination of the spinal fluid with a detergent washing agent.

However, other authors attributed the meningitis directly to the dye: Worthington et al. ([\[5\]](#)) reported a case of acute chemical meningitis after metrizamide myelography; Sand et al. ([\[6\]](#)) described 7 similar cases.

Worthington and colleagues remarked that whilst "rare" these cases warranted being

"followed carefully for possible later sequelae."

White ([\[7\]](#)) described a further case of metrizamide meningitis arising 24 hours after myelography and presenting with fever, nuchal rigidity, vomiting, and mental confusion .

Spinal fluid cultures were negative.

In 1985, DiMario reported on a case of aseptic meningitis secondary to metrizamide in a small infant (age 4 and half months). ([\[8\]](#))

In Belgium, a case of meningitis following iohexol was reported in 1991([\[9\]](#)). Iohexol was a popular and widely-used water-based dye that largely replaced older ones and was regarded as safe.

Norwegian authors Bo, Nestvold and Sortland ([\[10\]](#)) also described 2 cases of meningitis following iohexol used in the mid-1990s.

As the previous authors, they remarked that clinically the presentation was indistinguishable from that of bacterial meningitis.

Forgacs et al. ([\[11\]](#)) noted a series in The Netherlands, which found a 3% incidence of bacterial meningitis after transphenoidal surgery.

They also noted that drugs administered to microsurgical patients can cause chemical meningitis.

These included: NSAIDs, antibiotics (sulphonamides, penicillins) gamma globulin and OKT3.

Comparing infectious and non-infectious causes, the authors looked at 70 consecutive patients with post-operative meningitis, of which 27 met the criteria for chemical meningitis (negative spinal fluid cultures and patient recovery without antibiotics), 13 bacterial and 20 were "indeterminant".

Cases of chemical meningitis showed raised white cell count in the CSF (but <7500) and glucose >10mg/dL).

They rarely had temperatures above 39.4°C and fever was of shorter duration than with infective meningitis.

They concluded that sterile meningitis is more common after posterior fossa surgery.

Other agents causing chemical meningitis include: gadolinium ([\[12\]](#)), baclofen ([\[13\]](#)), methotrexate ([\[14\]](#)), cytarabine: both systemic and intrathecal, ([\[15\]](#)); ([\[16\]](#)).

Recently, French authors Hoeffel et al. ([\[17\]](#)) reported a case of chemical meningitis after intrathecal injection of contrast media and hydrocortisone.

(They also described a case of intracranial haematoma after intrathecal injection of 125 ml of hydrocortisone acetate).

Intrathecal injection of steroid preparations, either methylprednisolone or hydrocortisone ([\[18\]](#) ; [\[19\]](#)) can cause chemical meningitis. Plumb and Dismukes ([\[20\]](#)) suggested:

"Steroid-induced chemical meningitis should be considered in any patient who develops CNS symptoms and an abnormal CSF after receiving intrathecal steroids."

Spinal anaesthesia may also cause chemical meningitis; various factors such as contaminants in the preparation, disinfectant, starch (in sterile gloves) have been implicated. ([\[21\]](#))

In 1999, Lakhkar and Sinha reported in the Indian Journal of Radiology and Imaging, a case of a 6 year old boy treated for acute lymphoblastic leukaemia with intrathecal methotrexate, who developed hemiplegia and seizures due to an intracerebral bleed.

The authors noted that "transient" complications of IT-MTX include paresis, paraplegia and chemical arachnoiditis.

Also in 1999, Fukushima et al. ([\[22\]](#)) reported a case of chemical meningitis in a child undergoing CNS prophylactic treatment for acute lymphoblastic leukaemia. MR imaging showed diffuse pachymeningeal enhancement.

Inadvertent intrathecal injection of vincristine causes leptomeningitis and ventriculitis ([\[23\]](#)) that in some cases is fatal. Cerebrospinal lavage must be undertaken to reduce the damage.

Surviving cases may go on to have long-term problems as a result of the toxicity.

Other cases of aseptic meningitis can also arise.

Collard et al. ([24]) reported a case in a patient with familial Mediterranean fever (FMF), who had 6 episodes of aseptic meningitis within a 7 year period.

Mollaret's meningitis is a rare phenomenon, first described in 1944.

It refers to chronic recurrent aseptic meningitis, usually of unknown aetiology.

Thilmann et al. described ([25]) 2 cases of recurrent aseptic meningitis, one of whom had an initial episode after myelography with iopamidol, and a second after oral ingestion of the NSAID ibuprofen (400mg).

Indeed, ibuprofen has been reported a number of times as a cause of aseptic meningitis, especially in patients with Systemic Lupus Erythematosus; Horn et al. reported a case in a patient with rheumatoid arthritis ([26]), Pisani et al. ([27]) described 3 episodes over a period of 20 years, in an otherwise healthy patient, after taking ibuprofen.

The patient described by Thilmann suffered 5 attacks of meningitis in total, 2 of which were drug-related, the other 3 arising spontaneously.

Thilmann and colleague suggested that Mollaret-meningitis is a

“special form of a drug-induced allergic reaction, the provoking agent of which remains unknown.”

As Horn and colleagues pointed out, this may be linked to autoimmune conditions such as lupus and may thus have a particular relevance in arachnoiditis.

They concluded:

"Although persons with systemic lupus erythematosus appear to have an increased risk for this type of reaction, the development of signs and symptoms in other patients warrants the consideration of nonsteroidal antiinflammatory drugs as the cause of aseptic meningitis."

Japanese authors Kohira and Ninomiya ([28]) described a case of Mollaret meningitis with back pain, where herpes simplex virus type 2 was found in the CSF.

The 59 year-old woman had four episodes of recurrent self-limited aseptic meningitis, featuring acute headache, back pain, and nausea with fever, which resolved within 14-20 days.

Other causes of aseptic meningitis include events such as rupture of a pineal cyst ([29]) and intracranial epidermoid tumours ([30]).

Maignen et al. ([31]) suggested that various drugs (non-steroidal anti-inflammatory agents such as ibuprofen and sulindac, antibiotics such as cotrimoxazole, trimethoprim, ciprofloxacin and miscellaneous drugs such as carbamazepine, human immune globulin and muromonab CD3.) can be associated with development of aseptic meningitis and that patients with lupus or connective tissue disorders are at a higher risk.

They noted

"Meningeal symptoms occur a few hours after drug intake and resolve without sequelae within one or two days after drug withdrawal."

[1] Jolles S, Sewell WA, Leighton C. *Drug Saf* 2000 Mar; 22(3):215-26 Drug-induced aseptic meningitis: diagnosis and management.

[2] Curtin JA *Annals of Internal Medicine* 1971; 74: 838- Pantopaque hypersensitivity meningitis.

[3] McBeath AA, *JAMA* 1980; 243: 22-4 Eosinophilic meningitis following myelography

[4] Vik-Mo H, Maurer HJ. *Acta Radiol Diagn (Stockh)* 1975 Jan; 16(1):39-42 Meningeal

reactions following myelography. Effects of detergent washing agent.

[5] Worthington M, Callander N, Flynn R, Sullivan R. *Surg Neurol* 1983 May;19(5):456-8 Acute chemical meningitis after metrizamide-lumbar myelography.

[6] Sand T, Anda S, Hellum K, Hesselberg JP, Dale L. *Neuroradiology* 1986;28(1):69-71 Chemical meningitis in metrizamide myelography. A report of seven cases.

[7] White WB. *South Med J* 1984 Jan; 77(1):88-9 Metrizamide meningitis.

[8] DiMario FJ Jr. *Pediatrics* 1985 Aug; 76(2):259-62 Aseptic meningitis secondary to metrizamide lumbar myelography in a 4 1/2-month-old infant.

[9] Alexiou J, Deloffre D, Vandresse JH, Boucquey JP, Sintzoff S. *Neuroradiology* 1991;33(1):85-6 Post-myelographic meningeal irritation with iohexol.

[10] Bo SH, Nestvold K, Sortland O. *Tidsskr Nor Laegeforen* 1995 Sep 10;115(21):2646-7 [Meningitis after myelography]

[11] Forgacs P, Geyer CA, Freidberg SR *Clinical Infectious Diseases* 2001; 32(2): 179-185 Characterization of Chemical Meningitis after Neurological Surgery

[12] Eustace S, Buff B *Canadian Association of Radiologists Journal* 1994; 45(96): 463-5 Magnetic resonance imaging in drug-induced meningitis.

[13] Naveira FA, Speight KL, Rauck RL, Carpenter RL *Anesthesia & Analg* 1996; 82(6): 1297-9 Meningitis after injection of intrathecal baclofen.

[14] Mott MG, Stevenson P, Wood CB *Lancet* 1972; ii: 656- Methotrexate meningitis

[15] Thordarson H, Talstad I *Acta Medica Scand* 1986; 220(5_ : 493-5 Acute meningitis and cerebella dysfunction complicating high-dose cytosine arabinoside therapy.

[16] Obwegeser A, Seiwald M, Stockhammer G *Journal of Neurosurg* 1998; 89(1): 172-3 Intraventricular chemotherapy.

[17] Hoeffel C, Gaucher H, Chevrot A, Hoeffel JC. *J Spinal Disord* 1999 Apr; 12(2):168-71 Complications of lumbar puncture with injection of hydrosoluble material.

[18] Gutknecht DR *Am J Med* 1987 March; 82(3): 570 Chemical meningitis following epidural injections of corticosteroids.

[19] Stratton I *Med J Aus* 1975; 2: 650 Dangers of intrathecal hydrocortisone sodium succinate.

[20] Plumb VJ, Dismukes WE *South Med J* 1977 Oct ; 70(10): 1241-3 Chemical meningitis related to intrathecal corticosteroid therapy

[21] Gibbons RB *JAMA* 1969 Nov 3; 210(5):900-2. Chemical meningitis following spinal anaesthesia.

[22] Fukushima T, Sumazaki R, Koike K, Tsuchida M, Okada Y, Maki T, Hamano K. *Ann Hematol*

1999 Dec;78(12):564-7 A magnetic resonance abnormality correlating with permeability of the blood-brain barrier in a child with chemical meningitis during central nervous system prophylaxis for acute leukemia.

[23] Al Ferayan A, Russell NA, Al Wohaibi M, Awada A, Scherman *Childs Nerv Syst* 1999 Mar;15(2-3):87-9B. Cerebrospinal fluid lavage in the treatment of inadvertent intrathecal vincristine injection.

[24] Collard M, Sellal F, Hirsch E, Mutschler V, Marescaux C. *Rev Neurol (Paris)* 1991;147(5):403-5 [Recurrent aseptic meningitis in periodic disease or Mollaret's meningitis?]

[25] Thilmann AF, Mobius E, Thilmann RR, Topper R. *Fortschr Neurol Psychiatr* 1991 Dec;59(12):493-7 [Recurrent aseptic meningitis (Mollaret meningitis)--spontaneous and drug-induced origin]

[26] Horn AC, Jarrett SW. *Ann Pharmacother* 1997 Sep; 31(9):1009-11 Ibuprofen-induced

aseptic meningitis in rheumatoid arthritis.

[27] Pisani E, Fattorello C, Leotta MR, Marcello O, Zuliani C. *Ital J Neurol Sci* 1999 Feb;20(1):59-62 Recurrence of ibuprofen-induced aseptic meningitis in an otherwise healthy patient.

[28] Kohira I, Ninomiya Y. *Rinsho Shinkeigaku* 2002 Jan;42(1):24-6[A case of recurrent aseptic meningitis (Mollaret meningitis) with back pain in which was detected the DNA of herpes simplex virus type 2 in cerebrospinal fluid]

[29] Kitayama J, Toyoda K, Fujii K, Ibayashi S, Sugimori H, Sadoshima S, Fujishima M. *No To Shinkei*

1996 Dec;48(12):1147-50 [Recurrent aseptic meningitis caused by rupture of a pineal cyst]

[30] Becker WJ, Watters GV, de Chadarevian JP, Vanasse M. *Can J Neurol Sci* 1984 Aug; 11(3):387-9 Recurrent aseptic meningitis secondary to intracranial epidermoids.

[31] Maignen F, Castot A, Falcy M, Efthymiou ML. *Therapie* 1992 Sep-Oct;47(5):399-402 [Drug-induced aseptic meningitis]