

Antibiotic induced meningitis

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Abstract

Three patients with antibiotic induced meningitis, one following penicillin with seven episodes, are reported on—the first well documented description of penicillin induced meningitis. In this patient episodes of headache and nuchal rigidity appeared with and without CSF pleocytosis. Two patients had a total of five episodes of antibiotic induced meningitis after trimethoprim-sulphamethoxazole (co-trimoxazole) administration. The features common to all three patients were myalgia, confusion and low CSF glucose. CSF analysis was not a reliable method to differentiate antibiotic induced meningitis from partially treated bacterial meningitis.

(*J Neurol Neurosurg Psychiatry* 1994;57:705-708)

Drug induced meningitis has been reported following administration of various agents including antimicrobial drugs, cytotoxic drugs, non-steroidal anti-inflammatory drugs, and immune globulins.¹ Antibiotic induced meningitis has been reported mostly with sulphonamides. The symptoms develop a few hours to days after the exposure to the antibiotic and include headache, nausea, myalgia, chills, fever, and confusion.^{1,2} Typical CSF findings consist of polymorphonuclear pleocytosis, normal glucose, and elevated protein. The first well documented case of penicillin induced meningitis is described, together with two more cases of co-trimoxazole induced meningitis with unusual presentations. It was suggested that the levels of CSF glucose can aid in the differentiation between drug induced meningitis and partially treated

bacterial meningitis; low CSF glucose was regarded as a sign of partially treated bacterial meningitis.² The authors' experience and review of the literature do not support this notion and a different management approach is suggested.

Patients and methods

PATIENT 1

An 82-year-old woman had seven episodes of meningitis from 1984 to 1991 (table 1). In her seventh episode she was admitted to the Neurology Department at the authors' hospital with fever, myalgia, and headache. A week before admission, her family physician prescribed amoxicillin 1.5 g daily because of dyspnoea, cough, fever, and right upper lobe pneumonia. The patient did not improve and developed severe headache, myalgia, and confusion within two days. On admission, her temperature was 38.7°C and nuchal rigidity was found. Fine râles were heard over the lower lung fields. Neurological examination revealed only somnolence and very mild confusion. CSF was clear under normal opening pressure with high protein, low level of glucose, and 20 polymorphonuclear (PMN) cells (table 1). CSF Gram stain and culture were negative. Blood count showed $13.5 \times 10^9/l$ white blood cells (WBCs) (95% polymorphonuclear cells). The patient was treated with intravenous ceftriaxone (2 g/day), on the assumption that she had a partially treated meningitis, and recovered fully within four days. A repeat CSF examination was normal.

Meticulous investigation of the patient's medical records showed that, on six previous occasions, penicillin or amoxicillin had been administered 2-5 days before each admission

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Received 28 July 1993
and in revised form
21 September 1993.

Accepted 30 September 1993

Table 1 Symptoms, signs and CSF in patient 1 with recurrent penicillin induced meningitis

Date	Episodes of meningitis on:						
	1/84	2/85	3/87	3/87	2/89	4/91	12/91
Clinical data:							
Headache	+	+	+	+	+	+	+
Myalgia	?	-	+	-	+	+	+
Fever	+	+	-	+	+	+	+
Confusion	?	+	+	+	+	+	+
Nuchal rigidity	+	+	+	+	+	+	+
Latency*	?	5	2	?	4	3	2
CSF:							
Cells (mm ³)							
PMNs	36	0	0	0	0	4800	20
Lymphocytes	10	0	0	0	5	640	0
RBCs	0	0	30	0	15	0	6
Protein (mg/l)	1020	3050	2610	955	2074	2560	1380
Glucose (mmol/l)	3.9	3.6	3.0	3.8	2.8	2.6	3.1
Serum glucose (mmol/l)	?	6.2	6.4	7.8	6.0	5.0	6.3

*Latency period (in days) from the exposure to the drug to the appearance of symptoms.

for meningitis. This treatment was given for presumed or confirmed diagnosis of upper respiratory tract infection, sinusitis, or urinary tract infection. Each time, the patient had myalgia, headache, confusion, fever, and nuchal rigidity (table 1). CSF examination showed high protein levels in all episodes, low CSF glucose, and pleocytosis in four episodes. No organisms were seen in any of the Gram or Ziehl-Neelsen stained preparations, and all cultures (for bacteria, fungi, or viruses) remained sterile. Cytological examination of CSF was compatible with meningitis; malignant cells or Mollaret cells were not found. The following laboratory examinations were normal (these examinations were part of an extensive investigation over a period of seven years): liver and kidney function tests, serum electrolytes, thyroid function tests, and coagulation studies. Anti-nuclear factor, latex, Rose Waller, immunoelectrophoresis, protein electrophoresis, anti-DNA, anti-Sm, anti-Ro, anti-La, anti-thyroglobulin were all negative. Serology for herpes simplex virus, Epstein-Barr virus, cytomegalovirus lymphocytic choriomeningitis, mumps, leptospira species, brucellosis, and the Widal test were negative. Blood count at the acute phase always showed leucocytosis without eosinophilia and normochromic/normocytic anaemia. Serum ferritin and iron were normal. Bone marrow examination was normal.

Brain CT and MRI scans were normal. EEG showed slowing of background activity correlated with the confusion (in all episodes), but this reverted to normal when the patient recovered. In four of the episodes the patient was treated with either chloramphenicol or ceftriaxone. After the last episode, the patient was advised not to use penicillin, and she has had no recurrence of meningitis in more than one year of follow up.

PATIENT 2

A 15-year-old, previously healthy boy was treated with co-trimoxazole for a urinary tract infection. Three days later he developed fever with severe myalgia of the hip muscles, headache, and vomiting. On examination, his temperature was 39°C and nuchal rigidity was found. The rest of the neurological examination at this point was normal. CSF contained 590 PMNs/mm³, 50 lymphocytes/mm³, and five red blood cells/mm³, cultures were negative. CSF protein and glucose were 120 mg/dl and 2.2 mmol/l respectively (blood glucose was 5.8 mmol/l). Co-trimoxazole was stopped and the patient was given chloramphenicol for a tentative diagnosis of partially treated meningitis. Seven hours later acute paraparesis and urinary retention with a D11 sensory level appeared. CT myelography was normal. Three days later the patient was paraplegic with a D8 sensory level, prominent nystagmus to all directions, right internuclear ophthalmoplegia, and bilateral facial and left hypoglossal nerve palsies. He required mechanical ventilation because of CO₂ retention. Intravenous high dose steroids were administered. Gradual resolution of brain-

stem signs occurred, but the paraparesis improved only to a very limited extent.

Three months later the patient (in a wheelchair) was again treated with co-trimoxazole for a urinary tract infection. Nuchal rigidity, paraplegia, and multiple cranial nerve palsies reappeared within one day. The patient was treated with high dose steroids with partial resolution of his signs. CSF examination revealed a protein level of 230 mg/dl and glucose level of 3 mmol/l (blood glucose 6 mmol/l); there were 4750 PMNs/mm³ and 1000 lymphocytes/mm³. CSF Gram stain was negative and the cultures were sterile. Laboratory findings during the two hospitalisations showed normal liver and kidney function tests, and coagulation studies. Serological tests for HIV, mycoplasmae, brucella, measles, Epstein-Barr virus, and cytomegalovirus were negative. Anti-nuclear factor was +4/4, anti-DNA 8 µg/ml (normal <1.5 µg/ml), and C3 level 43 mg/dl (normal >60 mg/dl). A direct Coombs' test was positive and a skin biopsy for lupus band test was positive. Brain CT and MRI scans were unremarkable. In two years of follow up the patient developed other typical manifestations of systemic lupus erythematosus, including anaemia, rash, thrombocytopenia, and arthritis.

PATIENT 3

A 71-year-old man was admitted because of fever with a temperature up to 39°C, chills, severe headache, and myalgia which developed 12 hours after sexual intercourse. On admission, the patient was somnolent and somewhat confused. Nuchal rigidity appeared only 24 hours later and a lumbar puncture was performed. The CSF looked turbid and the pressure was 30 cmH₂O (3kPa). CSF analysis revealed 2500 PMNs/mm³, protein 315 mg/dl, glucose 3.2 mmol/l (blood glucose 7.2 mmol/l), and no organisms on Gram stain. Peripheral blood count showed a leucocytosis with WBCs of 15.3 × 10⁹/l, of which 90% were PMNs. Empirical treatment with ceftriaxone (2 g/day) was administered for 10 days. The patient recovered completely within 48 hours. CSF, blood, throat, and urine cultures remained sterile. One month later the patient was admitted again with similar signs and symptoms. Nuchal rigidity, Kernig's, and Brudzinski's signs were detected on admission. Lumbar puncture showed a turbid fluid under an increased opening pressure with 640 PMNs/mm³, 10 lymphocytes/mm³ and 70 RBCs/mm³. Protein was 390 mg/dl, glucose 3 mmol/l (blood glucose 6 mmol/l); CSF cultures were negative. The patient was started immediately on intravenous ceftriaxone (2 g/day) and recovered within 72 hours.

After repeated questioning about drug consumption the patient admitted that his primary physician instructed him to take a tablet of co-trimoxazole (400 mg/80 mg) half an hour after sexual intercourse, because he had been suffering from recurrent urinary tract infection.

Only one tablet of co-trimoxazole was ingested 12 and 5 hours respectively before each of the two admissions. The patient recalled a third episode of milder symptoms after co-trimoxazole ingestion, which occurred one month before his first admission to the hospital. On extensive investigation of the possible causes of recurrent meningitis, which included liver function tests, serum protein electrophoresis, anti-nuclear factor, CSF and blood VDRL, and C3 complement levels were all normal. CSF and blood serology for herpes simplex virus, Epstein-Barr virus, cytomegalovirus, toxoplasma and cryptococcal antigen were negative. Multiple blood, urine, and faeces cultures, including cultures for mycobacteria, were negative. CT and MRI studies of the brain, base of skull, lumbar, and thoracic spine were normal apart from an old right basal ganglion lacunar infarct. The patient was instructed to avoid trimethoprim or sulphonamides. No recurrent episodes occurred during one year of follow up.

Discussion

Drug induced meningitis has been described following the exposure to several drugs and chemicals. The mechanisms proposed involve either a direct chemical irritation or a hypersensitivity reaction.¹ The benign nature of drug induced meningitis, and the progressively shorter time interval between ingestion of the drug and the appearance of symptoms on drug re-exposure, indicate that an allergic mechanism is involved. However, there are very few reports which support the immunological nature of this complication. In ibuprofen induced meningitis, a specific cell mediated response was measured by a macrophage migration inhibition test.³ Immune complexes were found intrathecally in one case of ibuprofen induced meningitis,⁴ but not in another.⁵

Antimicrobial drug induced meningitis has been described most frequently with co-trimoxazole.^{1,2} Single cases of isoniazid and ciprofloxacin induced meningitis have been reported (table 2).^{6,7}

The first patient presented here is the only well documented case of penicillin induced meningitis. This patient had six episodes of meningitis before the true aetiology of her recurrent disease was recognised following the

seventh episode. Each stereotypical episode followed penicillin ingestion by only few days (see table 1). Of note are low CSF glucose in four episodes, usually with CSF pleocytosis. In three milder episodes nuchal rigidity, headache, and fever were not accompanied by CSF pleocytosis.

The patient had signs of CNS involvement, namely, confusion and alteration of the EEG in all episodes.

Farmer *et al*⁸ reported a 47-year-old patient with a serum sickness-like reaction three days after injection of penicillin. Three months later she developed scleritis and 11 months later severe occipital headache, vertigo, tinnitus with papilloedema, and CSF lymphocytic pleocytosis. Biopsy of the dura showed that it was thickened and infiltrated with plasma cells and eosinophils. The authors suggested that the patient had penicillin induced pachymeningitis. This case report is markedly different from the present case and from previous reports of drug induced meningitis. The time interval between a single penicillin injection and meningitis was 11 months, more than can be expected for classic drug induced meningitis. The dural biopsy was compatible with an allergic mechanism, but no other facts support the possible link to penicillin—for example, drug re-exposure.

Hypersensitivity reactions are the most common adverse effects of the penicillins. They can cause rash, fever, vasculitis, and other allergic side effects which are probably mediated by antibodies created against proteins covalently bound to penicillin.⁹ The allergic mechanism in penicillin induced meningitis might involve the deposition of immune complexes in the meninges, an intrathecal cell mediated or humoral response to proteins bound to penicillin, and a chemical arachnoiditis similar to that observed in direct intrathecal injection of penicillin.^{9,10}

The additional cases of co-trimoxazole induced meningitis presented have some unique features. It is known that co-trimoxazole can cause several CNS untoward effects such as headache, depression, and hallucinations.⁹ In addition, there have been several reports of recurrent aseptic meningitis caused by repeated exposure to co-trimoxazole.^{2,11,12} The typical features of co-trimoxazole induced meningitis include chills, myalgia, facial oedema, and confusion. Meningitis appears within several hours following ingestion of the drug. CSF usually shows PMN pleocytosis with elevated protein and normal glucose.²

The second patient presented with recurrent co-trimoxazole induced meningoencephalitis following co-trimoxazole ingestion, with serological evidence of systemic lupus erythematosus. The causative role of co-trimoxazole is supported by the abrupt onset of meningitis soon after taking the medication on two occasions.

The authors believe that the antimicrobial drug directly triggered meningoencephalitis rather than this being a case of CNS lupus with meningeal involvement. This is supported by

Table 2 Antibiotic induced meningitis

Antibiotic	No. of patients	References
Co-trimoxazole *	20†	1, 2, 10, 12, 14, 19
Trimethoprim	6	1, 2, 15
Sulphonamides‡	3	1, 2, 20
Isoniazid	1	5
Ciprofloxacin	1	4
Penicillin	1	Present study

*Co-trimoxazole.

†Including the present patients.

‡Sulphonamides other than sulphamethoxazole.

two facts: (1) in each episode clear-cut signs of meningitis preceded the neurological deterioration; (2) the CSF PMN pleocytosis is compatible with drug induced meningitis rather than CNS lupus, in which lymphocytic pleocytosis is the typical finding.¹³ Previous reports described autoimmune disorders in seven of 18 patients with trimethoprim or co-trimoxazole induced meningitis.¹⁴ Four of the patients had systemic erythematosus, one following trimethoprim only,¹⁵ and three following co-trimoxazole.^{2,14,16} This present report suggests that patients with systemic lupus erythematosus are not only at a greater risk for developing drug induced meningitis,^{2,5,14-19} but they are possibly at risk of undergoing drug induced exacerbation of their autoimmune disease.

The third patient had many features in common with other patients with antibiotic induced meningitis, but he also showed some unusual features: (1) clinical context—the antibiotic was taken prophylactically with no suggestion of infection which triggered recurrent postcoital meningitis; (2) low glucose levels in the CSF—in other reports of co-trimoxazole induced meningitis, normal glucose level was the rule. This was considered important in the differentiation of bacterial from drug induced meningitis, although low CSF glucose has already been reported in ibuprofen and immune globulin induced meningitis,^{5,7,20} and in three patients with co-trimoxazole induced meningitis.^{2,14} Thus, according to the literature and the experience cited in this paper, low CSF glucose is not a rare finding in drug induced meningitis and should not be taken as a clue to the diagnosis of either antibiotic induced or bacterial meningitis.

What are the chances that a patient who develops recurrent meningitis during treatment with antibiotics may have drug induced meningitis rather than a partially treated bacterial meningitis? Apart from with co-trimoxazole, antibiotic induced meningitis is rare and should be a diagnosis of exclusion. Thus, in patients with recurrent CSF PMN pleocytosis and low CSF glucose who are suspected of having antibiotic induced meningitis, antibiotics should not be discontinued, but switched to another class. This should be the first step and should be followed by diagnostic measures to rule out other causes of recurrent meningitis.

Conclusions

Penicillin, along with other antimicrobial agents, can cause recurrent meningitis. Co-trimoxazole should be avoided in patients with systemic lupus erythematosus because it may provoke recurrent CNS relapses of their autoimmune disease. Patients with drug-induced meningitis might have CSF PMN pleocytosis and low CSF glucose, so CSF analysis is not a reliable method for differentiation between drug induced meningitis and other causes of recurrent bacterial or aseptic meningitis.

This work was supported in part by the Lena P Harvey Endowment Fund for Neurological Research and by the Dr Benjamin and Adeline Boshes Endowment Fund.

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