CASE REPORT

Recurrent case of ibuprofen-induced aseptic meningitis in mixed connective tissue disease

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SUMMARY

Although relatively uncommon, the incidence of non-steroidal anti-inflammatory drug-induced aseptic meningitis appears to be increasing among patients with connective tissue disease and also among the healthy population. Ibuprofen is the most common culprit identified. We report a case of a 28-year-old woman with mixed connective tissue disease and recent intake of ibuprofen, presenting with a recurrent episode of ibuprofen-induced aseptic meningitis.

BACKGROUND

Meningitis associated with non-steroidal anti-inflammatory drug (NSAID) use appears to be relatively uncommon. However, its incidence seems to be increasing, mainly among patients with underlying autoimmune connective tissue disorder. Ibuprofen is the most frequently implicated culprit for drug-induced aseptic meningitis.

The possibility of ibuprofen-related meningitis or meningoencephalitis must be considered in patients taking ibuprofen, especially if they have an underlying autoimmune connective tissue disorder and if it is recurrent. We emphasise that it might be appropriate to screen for autoimmune diseases in previously healthy patients diagnosed with ibuprofen-related meningitis or meningoencephalitis.

CASE PRESENTATION

A 28-year-old woman with a history of mixed connective tissue disease on low-dose prednisone and ibuprofen presented with a history of high-grade fever, frontal headache, nausea and generalised bodyaches for 1 day. She had been taking ibuprofen 600 mg two to three times a day for the past 2 days for her arthralgia. Physical examination revealed an alert lady in no acute distress. She had a temperature of 103°F and she was hypotensive on presentation. Neck flexion was slightly limited because of pain. Kernig's and Brudzinkski's signs were absent and no focal neurological deficits were elicited on exam.

INVESTIGATIONS

She had a white cell count of 11 700/ μ l. Plain chest radiograph and calcium levels were within normal limits. Lumbar puncture was pursued and cerebrospinal fluid (CSF) analysis revealed a clear, colourless fluid with a white cell count of 36/mm³ (99% polymorphs, 1% lymphocytes), glucose 62 mg/dl, total protein 49 mg/dl and no organisms seen on Gram stain. MRI was unremarkable with no evidence of connective tissue cerebritis. Also, the spinal fluid PCR for enterovirus, herpes simplex virus and

Lyme disease were negative. *Streptococcus pneumoniae* urinary antigen and influenza screen were also negative.

DIFFERENTIAL DIAGNOSIS

A differential diagnosis of bacterial, viral, fungal and aseptic meningitis related to mixed connective tissue disease (MCTD) was considered.

TREATMENT

She was started on broad-spectrum antibiotic coverage with cefepime, vancomycin and acyclovir for the possible infectious meningitis. The patient's symptoms were thought to be due to NSAID-induced aseptic meningitis based on her CSF profile (neutrophilic pleocytosis with negative bacterial, viral and fungal cultures), her history of MCTD, temporal relationship between ibuprofen use and symptom onset/resolution, and similar episode about 3 weeks ago which was also preceded by ibuprofen use for her joint pain. The antibiotics were subsequently discontinued after 3 days. She did not receive any NSAIDs during her hospital course and her condition gradually improved.

OUTCOME AND FOLLOW-UP

Her symptoms completely resolved with no neurological sequelae and she was discharged on seventh day of her admission. She was advised not to take NSAIDs and has not had a second recurrence as of now.

DISCUSSION

Aseptic meningitis is a rare adverse effect of ibuprofen.¹ The first case was reported in 1978 by Widener and Littman² who reported the case of a 26-year-old woman with systemic lupus erythematosus (SLE) presenting with headache, fever, chills and meningism after ibuprofen ingestion on four separate occasions. CSF analysis was consistent with aseptic meningitis and the diagnosis was confirmed with a drug rechallenge. Since then, an increasing number of cases have been reported. The majority of cases were diagnosed in patients with underlying rheumatological disorders, mainly systemic lupus erythematosus, and also in MCTD and rheumatoid arthritis.³ Although ibuprofen has been most commonly associated,^{4,5} other NSAIDs like diclofenac, sulindac, naproxen, ketoprofen, tolmetin, piroxicam and, more recently, rofecoxib and celecoxib have also been found to cause this type of meningitis.^{3,6,7}

The pathogenic mechanism of NSAID-induced aseptic meningitis remains unclear. It does not seem

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to be mediated either by the inhibition of prostaglandin synthesis⁷ or by the accumulation of ibuprofen's metabolites within the central nervous system (CNS), because the latency period after rechallenge is short.¹ Since there is an increased intrathecal synthesis of IgG and immune complex formation, a type III or IV hypersensitivity reaction confined to CNS has been postulated.^{5 8–10} Thus, a pre-existing autoantibody maybe activated by ibuprofen. It has also been suggested that the drug combines with a CSF protein that acts as a hapten, thus explaining the restriction of the inflammatory response to the meningeal compartment.¹¹ Our patient's course was consistent with the hypersensitivity theory as the latency period was shorter during the second exposure and the symptoms were more severe. The higher incidence of ibuprofen-induced aseptic meningitis in patients with autoimmune disorders could be explained by the widespread use of NSAIDs or by their tendency to autoreact.¹

The signs and symptoms of NSAID-induced meningitis may become evident a few minutes to several hours after intake of NSAIDs. Common manifestations include fever, chills, headache, nausea, vomiting, generalised arthralgia/myalgia, nuchal rigidity and cutaneous rash (mimicking meningococcal disease).^{1 3 5 7 12} Classic signs of meningitis on physical examination may also be seen, including nuchal rigidity, and Kernig's and Brudzinski's¹³ signs. Patients can also have meningoencephalitis and present with confusion and upgoing plantar reflexes.¹¹

CSF usually shows pleocytosis with neutrophilic predominance; protein levels are frequently high, although normal in our case.^{1 2 5 13} Therefore, these may initially be confused as bacterial meningitis. In fact, our patient presented with a similar CSF picture, leading to a diagnosis of bacterial meningitis, and antimicrobial therapy was started. This is unlike aseptic meningitis associated with connective tissue disease which is usually lymphocytic.¹² However, occasionally, CSF may contain a significant percentage of lymphocytes and eosinophils in drug-induced aseptic meningitis.^{5 14} CSF glucose levels are usually normal in NSAID-induced meningitis, although moderately low levels may occur, but they have not been found to be close to 0 mg/dl as in acute bacterial meningitis.¹ The occurrence of coma and focal neurological deficits may suggest a viral meningoencephalitis syndrome.¹ The clinical course of ibuprofen meningitis or meningoencephalitis is relatively short and benign, with rapid resolution of symptoms after discontinuing the drug. However, CSF findings may return to normal slowly.¹ Cognitive or neurological sequelae have not been reported.⁴

NSAID-induced meningitis is a diagnosis of exclusion. Infectious agents and other non-infectious causes such as CNS tumours, metastatic carcinomas, sarcoidosis, SLE and granulomatous angiitis should be ruled out. A temporal relationship between the timing of ingestion of the drug and the onset of symptoms as well as response to rechallenge can support the diagnosis. However, rechallenge is not indicated, as re-exposure can lead to more severe symptoms as in our case. The symptoms may take days to develop after the first exposure to the drug, but repeated exposures to the drug can demonstrate a quicker onset of symptoms, usually within hours.^{4 15} Patients must be informed to avoid re-exposure to all drugs from the NSAID family, because there are reports of patients with recurrent episodes of aseptic meningitis due to different NSAIDs.¹ Correlation between the severity of underlying autoimmune disorders and the occurrence of NSAID-induced meningitis has not been established. Also, it does not seem to be dose dependent and has been reported in over the counter doses as well as high doses.

In conclusion, NSAID-induced aseptic meningitis is extremely rare; however, the widespread use of ibuprofen, as well as other

NSAIDs, particularly for rheumatological diseases, makes it an increasing possibility. Ibuprofen is the most frequently implicated drug in aseptic meningitis induced by drugs. The clinical course as well as CSF findings may be similar to that of acute bacterial meningitis, so it should be considered in the differential of patients, mainly with underlying autoimmune connective tissue disorders, and in patients with recurrent meningitis. In fact, NSAID-induced meningitis must be considered in any case of recurrent aseptic meningitis, and it may be appropriate to screen for autoimmune diseases in healthy subjects developing this.

Learning points

- The clinical course as well as cerebrospinal fluid findings of non-steroidal anti-inflammatory drugs (NSAIDs)-induced aseptic meningitis may be similar to that of acute bacterial meningitis. It should be considered in the differential diagnosis of patients with underlying autoimmune connective tissue disorders and recurrent aseptic meningitis.
- It may be appropriate to screen for autoimmune diseases in healthy subjects developing NSAIDs-induced aseptic meningitis.
- Patients developing this should avoid all types of NSAIDs as these have been described with many NSAIDs and a recurrence can be more severe.

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Competing interests None.

Patient consent Obtained.

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