Cognitive decline with chronic meningitis secondary to a COX-2 inhibitor

DAVID ASHTON, PETER KIM, NEIL GRIFFITHS, ROY BERAN

Department of Neurology, Liverpool Hospital, Sydney, Australia

This paper was presented on 13 May, 2003 at the Australian Association of Neurologists Scientific Congress, Sydney, Australia.

Address correspondence to: R. Beran, 12 Thomas Street, Suite 5, 6th Level, Chatswood, NSW 2067, Australia.
Fax: (+61) 2 9413 1353. Email: Roy.Beran@unsw.edu.au

Abstract
Non-steroidal anti-inflammatory drugs are currently being investigated as agents to reduce the incidence and progression of Alzheimer's disease. Paradoxically they have also been reported to induce deleterious effects on the central nervous system, including aseptic meningitis and cognitive decline in the elderly. We report a case of a 72-year-old woman who presented with a 6-week history of profound confusion whilst being treated with rofecoxib, a COX-2 inhibitor. Lumbar puncture demonstrated a lymphocytic pleocytosis with increased protein and normal glucose. Complete clinical remission occurred 5 days after the rofecoxib was ceased with no other cause found despite extensive investigation. This case illustrates that non-steroidal anti-inflammatory drugs, including the new COX-2 inhibitors, can produce chronic lymphocytic meningitis, which may manifest as cognitive decline. This mechanism may account for other case reports and epidemiological evidence of the association between non-steroidal anti-inflammatory drugs and confusion.

Keywords: COX-2 inhibitor, chronic lymphocytic meningitis, pseudodementia

Case history
A 72-year-old caucasian woman presented with a 6-week history of slowly progressive confusion. She had previously been living independently in the community and had normal premorbid cognitive function. She had no insight into her cognitive decline, which was noticed by her family. Her medical history included hypertension, which was controlled with trandolapril. The patient also had generalised osteoarthritis, treated with oral rofecoxib 25 mg daily for 6 months preceding admission. She did not consume alcohol or smoke.

On examination the patient had a Mini-Mental State Examination (MMSE) score of 15 out of 30. There were marked deficits in orientation, concentration and memory. There was no neck stiffness or fever and Kernig's sign was negative. The patient was afebrile and there were no focal neurological deficits. Her full blood count, electrolytes, renal function, arterial blood gas, urine and blood cultures, erythrocyte sedimentation rate and chest X-ray were all within normal limits. An electroencephalogram was consistent with a moderately severe encephalopathy. Imaging with CT and MRI of the brain was normal. A lumbar puncture was performed and the white cells were elevated at 221 × 10⁶/l, with lymphocyte predominance. The cerebrospinal fluid (CSF) protein measured 1.53 g/l and the CSF glucose was 3.0 mmol/l. Rofecoxib was ceased in light of the CSF findings. No antibiotics or antivirals were commenced. Two days later the MMSE of the patient had improved from 15 to 26, and thence to 30 after a further 3 days.

Extensive investigation was undertaken to elucidate potential causes of lymphocytic meningitis. Polymerase chain reaction on the CSF for herpes simplex, enterovirus and Mycobacterium tuberculosis were negative on two samples. Viral and bacterial cultures did not grow any organisms. Serology for syphilis, cryptococcal antigen, Dengue, Ross River, Barmah Forest, arbovirus, mumps, measles, rubella, HIV, cytomegalovirus and Epstein–Barr virus were performed on admission and repeated 6 weeks later and did not suggest any acute infections. Cytology of CSF showed lymphocytosis. Computed tomography of the chest and abdomen did not reveal evidence of sarcoidosis or malignancy. Lumbar puncture performed 2 weeks later reflected the clinical improvement as the white cell count had decreased to 70 × 10⁶/l and the protein level decreased to 0.9 g/l. At 3 months review the patient remained well with normal cognitive function.
Discussion

The differential diagnosis of aseptic meningitis is broad and includes viral, bacterial, fungal and parasitic infections, malignancy, drugs and autoimmune disease [1]. In this case, rofecoxib appeared to be the agent responsible as after a prolonged clinical illness the patient improved dramatically after cessation of the drug. The rapid rate of recovery, within 5 days, is characteristic of drug-induced meningitis rather than the 10–14 days that is typical for a viral meningitis [2]. Also, extensive investigation failed to reveal another aetiology and the improvement was maintained at follow-up. Rechallenging the patient with rofecoxib may have strengthened the evidence for causality. However, both the clinical team and patient agreed that it was not in the patient’s best interests to risk re-exposure given the availability of alternative analgesics to treat osteoarthritis.

The most common central nervous system (CNS) side-effects of non-steroidal anti-inflammatory drugs are tinnitus and hearing loss [3]. More serious side-effects are psychosis, aseptic meningitis, and cognitive dysfunction [3]. In 1982 Goodwin and Reagen described memory and concentration lapses after initiation of naproxen and ibuprofen, which resolved on discontinuation [4]. There are also two large prospective cohort studies, which have demonstrated longitudinal memory decline in high dose NSAID (non COX-2) users [5, 6]. In contrast, Rozzini [7] found that long-term NSAID use protected against dementia in another community-based cohort study. The author attributed part of this benefit to a decrease in multi-infarct dementia due to platelet inhibition [7]. NSAIDs may be protective against Alzheimer’s disease, as epidemiological studies have shown a negative correlation [8]. A small randomised controlled trial of NSAIDs in Alzheimer’s disease showed that indomethacin protected against cognitive decline. This effect is believed to be due to the blocking of inflammatory changes that have been observed in brains of Alzheimer’s disease patients including inflammatory cytokines and acute phase proteins [9]. The poor tolerability of NSAIDs alone or in combination with misoprostol in Alzheimer’s disease has led to interest in the use of selective COX-2 inhibitors such as rofecoxib [10]. In the future, large randomised controlled trials may help elucidate the overall influence of NSAIDs on cognition in various patient groups.

Aseptic meningitis is a rare side-effect of NSAID therapy [3]. The NSAIDs most commonly implicated are ibuprofen, sulindac, naproxen and tolmentin [3]. The selective COX-2 inhibitor rofecoxib, the aetiological agent in this case, has also recently been reported to induce this complication in five cases [11]. Patients in that report presented with prominent symptoms of acute meningitis including fever, neck stiffness and decreased level of consciousness, and had CSF findings of a polymorph predominant pleocytosis with increased protein [11]. This manner of presentation is typical for NSAID-induced meningitis [2]. In contrast, this patient had no clinical features of acute meningitis and the CSF was lymphocyte predominant. Review of Medline and Embase failed to produce any previous reports of this phenomenon. We postulate that if the initial clinical illness and presumably inflammation is less intense, as probable in our patient, then patients may continue to ingest the medication chronically and present insidiously with confusion rather than fever and headache and therefore be falsely diagnosed as having a chronic dementing process. Chronic ingestion of the drug will also lead to the accumulation of mononuclear cells and lymphocytes in the CSF. In a study of a strain of mice with autoimmune disease, lymphocytic meningitis developed if they were fed ibuprofen daily [2]. Aseptic meningitis has been described in a patient with ibuprofen-induced sensorineural hearing loss and thus may also be the mechanism for this more commonly recognised side-effect [12].

The pathogenesis of NSAID-induced aseptic meningitis is not known. A prostaglandin-mediated mechanism has been postulated but is considered unlikely as most patients can successfully tolerate another NSAID after developing aseptic meningitis [2]. An abnormal immune response isolated to the meninges has also been proposed and this has been supported by the finding of increased intrathecal IgG and immune complexes in some patients [13].

Aseptic meningitis and cognitive decline have previously been viewed as distinct pathological and clinical syndromes associated with NSAID use. In this patient the cognitive dysfunction appeared to be secondary to lymphocytic meningitis and we suggest that this mechanism may account for other case reports and epidemiological studies which have found NSAIDs to have deleterious effects on cognition. This patient had been on rofecoxib for 6 months and cognitive decline was particularly noted in the 6 weeks prior to admission. If the onset was slower, clinicians may be at risk of labelling such patients as having dementia and may fail to appreciate the reversible effects of these medications. We suggest that elderly patients have their cognition assessed regularly while taking NSAIDs and that NSAIDs should be considered as a possible cause for any cognitive decline. This causality could be assessed in individual cases by discontinuing the medication for a short period to observe the rapid improvement that characterises drug-induced meningitis.

Key points

- The new COX-2 inhibitors can produce an aseptic meningitis which may manifest as cognitive decline.
- Elderly patients should have their cognition assessed regularly whilst on NSAIDs.
- Suspicion of NSAID causality for cognitive impairment can be assessed by discontinuation of the drug.

Conflict of interest

None of the authors have any financial or proprietary interests in the aforementioned products.
Resolution of macroprolactinoma-induced symptomatic hydrocephalus following cabergoline therapy

PEDRO IGLESIAS¹, LUCÍA PÉREZ MACHO², JUAN J. DÍEZ³

Departments of ¹Endocrinology and ²Neurology, Hospital General, Segovia, Spain
³Department of Endocrinology, Hospital Ramón y Cajal, Madrid, Spain

Address correspondence to: P. Iglesias, Department of Endocrinology, Hospital General, Ctra. de Avila s/n, 40002 Segovia, Spain.
Fax: (+34) 921 419100. Email: piglesias@hgse.sacyl.es

Abstract

A 71-year-old man was referred because of memory loss. Magnetic resonance imaging showed a pituitary macroadenoma associated with hydrocephalus. Marked hyperprolactinaemia was present. After 2 months of cabergoline therapy, magnetic resonance imaging showed tumour shrinkage with resolution of the hydrocephalus. We report, for the first time, the adequate and rapid clinical response of a macroprolactinoma-induced symptomatic hydrocephalus in an elderly man to a low and once-a-week dose of cabergoline therapy. Medical therapy with this dopamine agonist in this particular patient was so effective that ventriculo-peritoneal shunting could be avoided.

Keywords: giant prolactinoma, cabergoline, hydrocephalus, hyperprolactinaemia