Trimethoprim-induced aseptic meningism

Introduction

Drug-induced aseptic meningism can occur following administration of a number of different pharmaceutical agents and has been seen in all age groups. Diagnosis is made on observation of the resolution of symptoms after drug withdrawal. The syndrome resolves quickly following drug cessation with little or no sequelae. Trimethoprim-induced meningism is a rare but important side effect that is not well known. This article highlights awareness of this condition.

Discussion

Drug-induced aseptic meningitis has been reported with several classes of drugs, including non-steroidal anti-inflammatory drugs, antibiotics and immunosuppressants (Capra et al, 2000; Meng and St Lezin, 2000; Ashwath and Katner, 2003). The most common antimicrobial implicated is trimethoprim-sulfamethoxazole and the second most common is trimethoprim alone (Morís and Garcia-Monco, 2014).

Predominance in patients with autoimmune disease, HIV and migraine has been noted (Pashankar et al, 1995; Jolles et al, 2000; Repplinger and Falk, 2011), as well as in women (Bruner et al, 2014).

Typically patients present with symptoms indistinguishable from early stages of infectious meningitis. CSF analysis can also mimic that of partially treated bacterial meningitis (Capra et al, 2000; Jolles et al, 2000). Typical CSF findings are elevated white cell count with polymorphonuclear predominance (Bruner et al, 2014; Morís and Garcia-Monco, 2014).

In this patient eosinophilia and raised levels of liver enzymes suggest the meningism may be part of a systemic hypersensitivity reaction. Other hypersensitivity reactions associated with trimethoprim include Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), hepatitis, anaphylaxis and uveitis.

There are no specific diagnostic tests, but in vitro lymphocyte transformation and interferon-gamma ELISpot assays may help with the diagnosis as in this patient. There are reports of recurrent episodes of drug-induced aseptic meningitis (Ashwath and Katner, 2003; Morís and Garcia-Monco, 2014), such as this case. Many involve repeat episodes of exposure, as the diagnosis was not made on first presentation, thus a thorough history is the best diagnostic tool. A trend

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CASE REPORT

A 34-year-old woman presented to the authors' service with a 3-day history of gradually worsening headache associated with photophobia. The headache was worse on lying flat and not relieved by simple analgesia. She was apyrexial. There was no rash present on admission, but non-pruritic erythematous papules developed on her face, neck, arms, legs and trunk within 24 hours of admission. She had been started on trimethoprim by her GP for a suspected urinary tract infection 3 days earlier. Examination revealed nuchal rigidity, tachycardia of 109 beats per minute and mild weakness on her left side resulting from a previous stroke secondary to a patent foramen ovale.

This patient had a similar admission 4 years previously. She attended the emergency department with the same symptoms of headache, vomiting, neck stiffness and photophobia. CSF analysis at the time of the previous admission was aseptic and she was discharged with a diagnosis of meningitis or meningism of unknown cause. She was also being treated with a course of trimethoprim for a urinary tract infection preceding this previous admission.

Past medical history included unexplained angioedema, an ischaemic stroke 2 years previously, a patent foramen ovale and migraine. At the time of admission she was on aspirin with antihistamine cover and simvastatin. She had a distant history of an anaphylactic reaction to a bee sting.

Investigations are listed in *Table 1*. Blood investigations revealed a neutrophilia, eosinophilia and lymphopaenia. C-reactive protein level was raised. Liver function tests revealed raised alkaline phosphatase, aspartate transaminase and γ-glutamyltransferase levels. Other laboratory studies were normal. Computed tomography of her head showed no change compared to the study done 9 months previously.

Lumbar puncture yielded clear colourless CSF. Opening pressure was 16 cmH_2O. Analysis of CSF revealed normal protein, glucose 4.2 mmol/litre, white cell count less than $5x10^9$/litre, and virology screen (cytomegalovirus DNA, Epstein–Barr virus DNA, enterovirus RNA, herpes simplex virus 1 and 2 DNA, varicella zoster virus DNA) was negative. CSF culture yielded no growth.

On admission, ceftriaxone and aciclovir treatment was initiated for suspected infectious meningitis. Intravenous fluids and analgesia were also administered for symptom management.

Owing to the aseptic CSF results, the temporal nature of the reaction to the course of trimethoprim and the history of a similar episode, a tentative diagnosis of trimethoprim-induced aseptic meningism was made. It is unclear whether the rash and raised liver enzyme levels were features of this reaction. Both resolved before discharge. The patient was discharged home after 5 days and made a full recovery. She has been advised to avoid trimethoprim and sulphonamides. In vitro lymphocyte proliferative and γ-interferon ELISpot assays performed 2 months after admission were consistent with sensitization to trimethoprim (*Figures 1* and *2*).

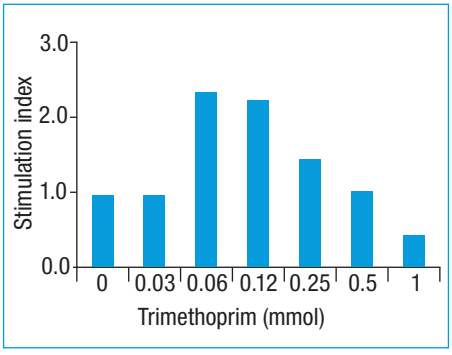
Table 1. Investigations

Inflammatory markers	White cell count	8.5x10^9/litre (4–11x10^9/litre)
	Neutrophils	7.21x10^9/litre (2.2–6.3x10^9/litre)
	Eosinophils	0.82x10^9/litre (<0.4x10^9/litre)
	Lymphocytes	0.27x10^9/litre (1–3.4x10^9/litre)
	C-reactive protein	147 mg/litre (<5 mg/litre)
Liver enzymes	Alkaline phosphatase	206 IU/litre (30–130 IU/litre)
	Aspartate transaminase	303 IU/litre (10–50 IU/litre)
	ϒ-glutamyl transferase	159 IU/litre (<55 IU/litre)
Radiology	Computed tomography head	Nil acute
Lumbar puncture	Appearance	Clear, colourless
	Opening pressure	16 cmH_2O
	Protein	270 mg/litre (250–450 mg/litre)
	Glucose	4.2 mmol/litre
	Culture	No growth
	Viral screen	Negative

towards increasing rapidity of onset and severity with each successive exposure to the offending drug has been noted (Pashankar et al, 1995).

Treatment involves stopping the offending medication. Meningeal symptoms subsided in the vast majority of patients without sequelae a few days after drug withdrawal (Meng and St Lezin, 2000).

Figure 1. Lymphocyte transformation test. Peripheral blood mononuclear cells, 1.5×10^5/well, isolated from patient's blood were incubated with trimethoprim (0.03–1 mmol) for 6 days. Radioactive [3H] thymidine was added for the final 16 hours of incubation, and T cell proliferation determined by [3H] thymidine incorporation using a beta counter.



The mechanism of drug-induced aseptic meningitis is not well understood. The postulated immune mechanism is a type III or IV hypersensitivity reaction (Pashankar et al, 1995; Repplinger and Falk, 2011). Antonen et al (1999) reported in-vitro production of interleukin-6 in response to trimethoprim in persons with trimethoprim-induced systemic reactions, and increased interleukin-6 but not IL-1β and TNFα in plasma and CSF in a patient with drug-induced aseptic meningitis (Antonen et al, 2001). Further research is warranted to establish the mechanism of this adverse effect. **BJHM**

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LEARNING POINTS

- Trimethoprim-sulfamethoxazole is the antimicrobial most commonly associated with drug-induced aseptic meningitis.
- Drug-induced aseptic meningitis can mimic the features of infectious meningitis.
- A thorough clinical history is the most important diagnostic tool.
- Treatment involves withdrawal of the causative medication.
- Most cases resolve without sequelae.

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Figure 2. Drug-induced interferon-gamma secretion. Peripheral blood mononuclear cells (5×10^5/well) were incubated with trimethoprim (0.03–0.5 mmol) or tetanus toxoid as a positive control for 48 hours in an ELISpot plate, pre-coated with interferon gamma capture antibody. ELISpot plate was then developed, and interferon-gamma secretion determined using an ELISpot plate reader. a. Interferon-gamma secretion as spot forming units (sfu). b. ELISpot images showing interferon-gamma expression.