Case Report

Aseptic meningitis after intrathecal baclofen injection

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Study design: Two case reports of aseptic meningitis after intrathecal baclofen injection.

Objectives: To report an unusual complication of intrathecal baclofen injection during test injections.

Setting: Department of Neurological Rehabilitation, R Poincaré Hôpital (Paris-Ile de France-Ouest University).

Case reports: We present two cases of chemical meningitis after intrathecal baclofen injections by lumbar puncture. These cases presented with febrile meningeal syndromes during the 24 h following intrathecal baclofen injection. Direct cerebrospinal fluid (CSF) examination and CSF cultures were negative. An intense cellular reaction was observed with a marked predominance of neutrophils. Meningitis resolved spontaneously over 3–4 days.

Conclusions: Chemical meningitis is a rare complication of intrathecal baclofen injections that must be recognized. It is a diagnosis of exclusion and its pathophysiological mechanism remains unclear.

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Keywords: intrathecal baclofen; chemical meningitis; complications

Introduction

Baclofen is a GABA_B receptor agonist, which reduces spasticity by blocking the monosynaptic reflex (Ia-motoneuron fibres)^{1,2} and certain polysynaptic reflexes in the spinal cord.^{3,4}

Intrathecal baclofen has been used since 1984 to treat spasticity refractory to oral antispastic drugs.⁵ The first indications for intrathecal baclofen consisted of spasticity secondary to spinal cord lesions (SCI and MS)^{5,6} and were subsequently extended to include spasticity secondary to supraspinal lesions (cerebral palsy, traumatic brain injury and stroke).^{7–9}

Before implanting an intrathecal baclofen infusion pump, test injections are performed to ensure the efficacy of baclofen and to confirm the indication for an implanted pump.

These injections are performed either by lumbar puncture or via an intrathecal site. Several complications can occur during this test phase, including a postlumbar puncture syndrome as well as infectious complications, such as bacterial meningitis. Some adverse effects can also be due to baclofen overdose, causing drowsiness, respiratory disorders and coma.

Only one case of aseptic meningitis has been described in the literature.¹⁰ We report two new cases of aseptic meningitis occurring after intrathecal baclofen injections.

Case No. 1

A 57-year-old woman, with a history of bilateral anterior cerebral artery infarct, was referred for intrathecal baclofen injection test. She presented severe spasticity of the lower limbs, despite oral antispastic treatment comprising baclofen (90 mg) and dantrolene (150 mg) for several months. The Ashworth score was 4/5 and the Penn spasm scale score was 4/4. She suffered severe functional impairment due to flexor spasms of the lower limbs associated with a spontaneous triple-flexion response. These spasms made lying in the supine position and sitting in a chair uncomfortable. Test intrathecal baclofen injections were started at a dose of 75 µg. This test dose was very effective, reducing the Ashworth score to 2/5 and the Penn spasm scale score to 1/4, together with pain relief. Transfers to bed and to a wheelchair were also clearly improved. At 24 h after the injection, the patient developed a febrile meningeal syndrome (headache, neck stiffness, nausea, vomiting associated with fever of 38.2°C). A lumbar puncture was performed and revealed hypercellularity with a

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predominance of neutrophils associated with raised cerebrospinal fluid (CSF) protein (2.23 g) and normal CSF glucose (Table 1). No eosinophils were observed in the CSF. Direct examination of CSF was negative. Blood tests revealed leukocytosis with CRP at 32 mg/l (CRP was 31 on the day before intrathecal injection) (Table 1). In this setting, it was decided to institute curative antibiotic treatment for iatrogenic meningitis (fosfomycine 3 g b.i.d. + cefotaxime 3 g q.i.d.). CSF culture was negative after 48 h and the antibiotics were discontinued. A progressive clinical improvement was observed with return to the baseline state on D3. CSF returned to normal on D6 and all cultures remained sterile. A diagnosis of chemical meningitis was adopted.

Case No. 2

A 39-year-old woman sustained a traumatic brain injury in July 2003 resulting in triplegia. She presented a severe motor deficit of the lower limbs and left upper limb, while the right upper limb was functional. She rapidly developed severe spasticity of the lower limbs, responsible for very poorly reducible extension of the lower limbs. The Ashworth score was 4/5 in the lower limbs and the Penn spasm scale score was 3/4. The spasticity was responsible for severe pain (spasms) and interfered with activities of daily life (sitting, personal hygiene, dressing). Oral antispastic treatments were ineffective. It

was then decided to perform test intrathecal baclofen injections in order to improve the patient's comfort. These injections were performed by lumbar puncture. During the first five injections performed at increasing doses (50, 75, 100, 100, 100 µg), the safety and efficacy of baclofen were excellent. The Ashworth score and the Penn spasm scale score decreased to 2/5 and 1/4, respectively, after injections of 100 µg. No adverse effect was reported. However, 24 h after the sixth injection, the patient developed a febrile meningeal syndrome (headache, neck stiffness, torpor, nausea, vomiting, fever of 38.5°C). Lumbar puncture revealed hypercellularity with a predominance of neutrophils (60%), raised CSF protein and normal CSF glucose. Direct examination of CSF was negative (Table 2). Blood tests revealed leukocytosis, but normal CRP. After discussion with infectiologists and intensive care physicians, it was decided not to treat this patient preventively, but to ensure close clinical and laboratory monitoring. Successive lumbar punctures revealed gradual reduction of the CSF cell count and CSF protein. CSF cultures remained negative. The meningeal syndrome and fever gradually resolved 24 h after onset of the symptoms, with complete resolution of all symptoms 3 days after onset of the disorders. CSF gradually returned to normal over two weeks. A diagnosis of chemical meningitis was adopted.

Discussion

Complications are very rare during test injections: postlumbar puncture syndrome, nausea, vomiting, urinary retention and, very rarely infectious complications. These infectious complications are exceptional during lumbar puncture injections and are more frequent during injections via an intrathecal site. In a retrospective study in neuro-radiologic procedures requiring lumbar puncture, the incidence of bacterial meningitis soon after a lumbar puncture was 0.2%.¹¹ The rate of meningitis reported in the literature with intrathecal catheters connected to subcutaneous ports, reservoirs or pumps was between 1 and 25%.¹² Only one case of aseptic or chemical meningitis after intrathecal baclofen injection has been described in the literature.¹⁰

Table 1 Clinical and laboratory course: Case No. 1

	D0	D1	D3	D6
Meningeal syndrome	+	+	—	—
Body temperature (°C)	38.5	38.2	37	37
Leukocyte count	15 400	13 170		5400
Neutrophils (%)	87	85		65
CRP (mg/l)	36	80		31
CSF protein (g/l)	2.23			0.4
CSF glucose (mmol/l)	3			2.9
Cells (/mm ³)	740			13
Direct examination	—			—
CSF culture	—			—

Table 2 Clinical and laboratory course: Case No. 2

	D0	D1	D3	D8	D11	D13	D15
Meningeal syndrome	+	+	+	—	—	—	—
Body temperature (°C)	38.6	38.7	37.8	37	37	37	37
Leukocyte count (/mm ³)	15 310	14 100	7600	6900	8750	6400	
Neutrophils	11 740	11 410	4900	3910	5550	3970	
CRP (mg/l)	1	4.9	10.6		8.5	48.2	
CSF protein (g/l)	1.88	3.53		2.97	2.42		1.93
CSF glucose (mmol/l)	2.9		1.3	1.9			2.4
CSF cytology (cell count with % of neutrophils)	1000	360075%		840	7		2
	60	75		65			
Direct examination	—	—	—	—	—	—	—
CSF culture	—	—	—	—	—	—	—

This case concerned a quadriplegic patient who received an injection of 75 µg of baclofen via a subarachnoid catheter. The clinical course was similar to the one observed in our patients with although a slightly earlier onset of febrile meningeal syndrome in the quadriplegic patient (10 h after injection). This syndrome resolved over 3–4 days.

Chemical meningitis has been described after the intrathecal injection of a large number of molecules. A review of the literature was published in 1937¹³ and comprised 200 cases of chemical meningitis secondary to intrathecal injections of anesthetic agents, lipiodol, serum and air. The most frequent cases were observed with isotope cisternography,^{14,15} intrathecal corticosteroid injections (hydrocortisone acetate, methylprednisolone acetate^{16–20} and methylprednisolone in a polyethylene glycol vehicle (Depomedrol®)²¹), aminoglycosides²² and spinal anesthetics.^{23,24} This led Merritt and Fremont-Smith to the conclusion that intrathecal injection of 'any foreign material may cause aseptic meningitis'.

The pathophysiology of chemical meningitis remains unclear. There are two proposed mechanisms of drug or chemical-induced aseptic meningitis:²⁵ one is a rare hypersensitivity-type reaction (allergic reaction), the other is chemical irritation. The first occurs frequently after oral treatment. The latter usually involves direct instillation of an agent into the CSF, generally by lumbar puncture.

There appears to be an association between the occurrence of the hypersensitivity reactions and underlying collagen vascular or rheumatologic disease.²⁶ No association appears to exist for the chemical irritation type of meningitis. Numerous drugs have been reported in the literature to cause aseptic meningitis. The nonsteroidal antiinflammatory drugs,²⁷ antimicrobials agents²⁸ and muromonab CD-3²⁹ are the most frequently implicated in hypersensitivity reactions. Aseptic meningitis resulting from chemical irritation of the meninges generally occurs after the instillation of the drug or chemical into the CSF. The most frequently implicated agents include corticosteroids, chemotherapeutic agents, detergents and radiographic agents. Aseptic meningitis symptoms are commonly fever, headache, nausea, vomiting and nuchal rigidity. The symptoms vary in severity and duration. Most patients recover fully within a few days without sequelae as in our cases. An analysis of the CSF shows leukocytosis with polymorphonuclear cells, increased protein, and normal glucose. In aseptic meningitis resulting from chemical irritation, recovery may be delayed depending on the duration of the contact of the medication with the meninges. The recommended management of the patients with suspected chemical meningitis²⁵ may include:

- Discontinuation of the suspected offending drug or chemical.
- Treatment with empiric antimicrobial agents until negative CSF culture results are known.

- Symptomatic treatments as needed.
- Subsequent rechallenge with drug (if hypersensitivity reaction is suspected) after determining that the risk–benefit ratio for a rechallenge is favorable.

Some elements are in favor of a direct irritation of meninges by baclofen. We have not found any reports in the literature of aseptic meningeal reaction in patients with continuous baclofen infusion pump. Chemical meningitis has only been described during direct intrathecal injections either by lumbar puncture or via an intrathecal site. Moreover, chemical meningitis has never been reported with oral baclofen. In the cases of hypersensitivity reactions, rechallenge with the drug is usually followed by recurrence of meningeal signs and symptoms within a few hours.²⁵ Our patients were treated with oral baclofen a few weeks after the chemical meningitis without meningitis recurrence.

We no longer systematically treat these cases of meningitis by antibiotics (Case No. 2) except in the presence of signs of clinical severity. We ensure close clinical and laboratory monitoring of patients with negative direct CSF examinations. Another element also appears to be important: inoculation meningitis rarely occurs so rapidly after intrathecal injection and would probably require a very large inoculate, while chemical meningitis usually occurs during the 24 h following injection.

Conclusion

Chemical meningitis is rare after intrathecal baclofen injection, as illustrated by the small number of published cases. However, this number is probably underestimated, as aseptic meningitis is often treated preventively by antibiotics due to the potential severity of meningitis. Chemical meningitis must be suspected in the presence of a febrile meningeal syndrome occurring during the 24 h following intrathecal injection with negative direct CSF examination. The pathophysiological mechanism of this meningitis remains unclear. A question remains unresolved: does a history of chemical meningitis constitute a contraindication to baclofen pump implantation? We have stopped trials and not implanted pumps to our patients after aseptic meningitis occurrence but we do not know if it is the right attitude.

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