

Ibuprofen-Induced Aseptic Meningoencephalitis Confirmed by Drug Challenge

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■ Abstract

Drug-induced aseptic meningitis (DIAM) is a diagnostic challenge. The major causative agents are nonsteroidal anti-inflammatory drugs (particularly ibuprofen), antibiotics, intravenous immunoglobulin, and OKT3 monoclonal antibodies. DIAM is more frequently observed in patients with autoimmune diseases. A 36-year-old woman was attended in our department 3 months after being diagnosed with aseptic meningoencephalitis. She had had 2 episodes in 9 months. Neurological symptoms were associated with ibuprofen. A challenge with acetylsalicylic acid was negative, whereas a drug challenge with ibuprofen was positive. Thirty minutes after ingesting 50 mg of ibuprofen, she experienced general malaise and progressively developed chills, fever (39.5°C), headache, and nuchal rigidity. Lumbar puncture showed normal glucose and high protein levels. Neutrophilic pleocytosis was observed at the first admission; lymphocytosis was predominant in the second and third episodes. DIAM is a rare and severe hypersensitivity reaction. Drug challenge enabled us to make an accurate diagnosis.

Key words: Drug allergy. Drug challenge. Drug-induced aseptic meningitis. Ibuprofen. Meningoencephalitis. Nonsteroidal anti-inflammatory drugs. Cerebrospinal fluid.

■ Resumen

La meningitis aséptica inducida por fármacos (MAIF) constituye un desafío diagnóstico. Los agentes etiológicos más frecuentes son los antiinflamatorios no esteroideos (especialmente ibuprofeno), antibióticos, inmunoglobulinas intravenosas y anticuerpos monoclonales OKT3. La MAIF aparece con más frecuencia en pacientes con enfermedades autoinmunes. Presentamos una paciente de 36 años que fue asistida en nuestro departamento 3 meses después de haber sido diagnosticada de meningoencefalitis aséptica. Había sufrido 2 episodios en 9 meses. Los síntomas neurológicos se habían asociado con ibuprofeno. La provocación con ácido acetilsalicílico fue negativa. La provocación medicamentosa con ibuprofeno fue positiva: treinta minutos después de 50mg de ibuprofeno sintió malestar general, y progresivamente temblores, escalofríos, fiebre >39.5°C, cefalea y rigidez de nuca. La punción lumbar mostraba una glucosa normal y un elevado nivel de proteínas. En el líquido cefalorraquídeo (LCR) de su primer ingreso se detectó una pleocitosis neutrofílica. En el LCR del segundo y en el tercer episodio se detectó una linfocitosis predominante. La MAIF es una rara y grave reacción hipersensibilidad. La provocación medicamentosa en nuestro caso permitió llegar a un diagnóstico preciso.

Palabras clave: Alergia a fármacos. Provocación medicamentosa. Meningitis aséptica inducida por fármacos. Ibuprofeno. Meningoencefalitis. Antiinflamatorios no esteroideos. Líquido cefalorraquídeo.

Introduction

Meningitis is usually produced by an infectious agent, although there are also multiple noninfectious causes. Aseptic meningitis is a central nervous system disease characterized by fever and meningeal symptoms with moderate, predominantly lymphocytic pleocytosis and bacteriologically sterile cultures [1]. It can be caused by viruses, drugs, and connective tissue disorders [1-3].

Drug-induced aseptic meningitis (DIAM) is a rare adverse reaction that constitutes a challenge for both diagnosis and patient management. The major causative agents are nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, intravenous immunoglobulin, and OKT3 monoclonal antibodies [2-5]. This type of drug hypersensitivity is more frequently observed in patients with a history of autoimmune diseases, particularly systemic lupus erythematosus [2,3,5]. Diagnosis is by exclusion of an infectious agent and other noninfectious causes and by demonstrating a convincing temporal relationship between ingestion of drugs and the onset of symptoms [2,3]. The recurrence of symptoms after rechallenge strongly supports the diagnosis of DIAM.

Case Description

A 36-year-old woman was attended in our allergy department 3 months after having been discharged from our hospital with a diagnosis of aseptic meningoencephalitis. It was her second episode of meningitis in 9 months, and her clinical picture was considerably more severe in this episode than in the first one, although resolution was faster. In 2006, she had received chemotherapy and biological agents for breast cancer, which was in remission. The patient was atopic and had been previously diagnosed with grass pollen-induced rhinitis. She had never had drug allergy.

Her first episode was in April 2009, when she was admitted to our hospital with a 48-hour history of headache, chills, fever (38.5°C), and nuchal rigidity. The headache was global and progressive. Symptoms were initially associated with an ear infection that was being treated with amoxicillin (3 oral doses of 500 mg daily). She added ibuprofen 400 mg to control her ear pain, and when her history was taken in the allergy department, she was sure that the neurological symptoms had begun 2 hours after the second or third dose of this drug. The patient underwent a physical examination, laboratory tests, lumbar puncture, and computed tomography (CT) (Table). She was then treated with intravenous cephalosporins and paracetamol, and her symptoms improved in 3 days. However, no bacterial or fungal microorganisms were detected, and serology testing revealed no signs of viral infection. Partially treated meningitis was the final diagnosis.

In the second episode (March 2010), she had taken an oral dose of ibuprofen 600 mg due to muscular pain with no signs of infection. Fifteen minutes after taking the drug she felt ill. She had fever (39.5°C) with intense headache that began after 30 minutes. She experienced confusion, unresponsiveness, psychomotor slowness, cognitive disturbances, nuchal rigidity, and right unilateral mild weakness of the limbs with no pyramidal signs. She was admitted to hospital and new tests were performed. No bacterial or fungal microorganisms were detected and serology testing revealed no signs of viral infection. Herpes simplex polymerase chain reaction and cerebrospinal fluid (CSF) enterovirus polymerase chain reaction were negative. CT of the brain was normal. The patient improved without specific treatment. Her general condition (including mental status and focal neurological signs) improved significantly, and after 3 days she was asymptomatic. She was diagnosed with viral aseptic meningoencephalitis. Ibuprofen was not considered to be the etiological agent.

Two months later, the family doctor referred her to our allergy department to investigate the implication of ibuprofen in these neurological episodes.

Table. Cerebrospinal Fluid Analysis and Clinical Picture

Date	First Episode	Second Episode		Third Episode (Drug Challenge)
	April 21, 2009	March 31, 2010	April 6, 2010	August 20, 2010
Glucose, mg/dL	57	73	58	60
Protein, mg/dL	113	213	55	99
White blood cells/mm ³	3600	378	18	200
Neutrophils, %	83%	35%		40%
Lymphocytes, %	17%	65%		60%
Red blood cells/mm ³	None	90	None	None
Culture	Negative	Negative	Negative	Negative
Onset of symptoms	60 min	15 min		30 min
Onset of fever	90 min	30 min		90 min
Time to lumbar puncture	5 h	2 h		3 h
Ibuprofen doses	400 mg	600 mg		50 mg
Recovery	72 h	72 h		24 h
Infection	Negative	Negative	Negative	Negative

Allergy Study

The clinical picture and the implication of ibuprofen led us to suspect an adverse drug reaction. However, the findings of the CSF analysis and the neurological diagnosis were controversial.

Skin prick and intradermal skin tests with ibuprofen 5 mg/mL (Pedeia, Orphan Europe SARL, Puteaux, France) were negative.

After obtaining written informed consent, we performed a challenge with acetylsalicylic acid, of which she tolerated 1000 mg. Consequently, hypersensitivity to NSAIDs was excluded. A challenge with amoxicillin, the antibiotic she was taking at the time of the first admission, was also negative.

Ibuprofen is an arylpropionic acid derivative and one of the most frequently used NSAIDs. After obtaining written informed consent, we performed a double-blind placebo-controlled drug challenge with ibuprofen. Thirty minutes after taking 50 mg (single dose), the patient experienced general malaise with headache. Sixty minutes later, she felt cold with shivers running down her spine. Ninety minutes after the dose, fever (39.5°C) with intense headache appeared, and she developed nuchal rigidity. She was admitted to hospital and a complete infection protocol was undertaken. Intravenous methylprednisolone (125 mg), dexchlorpheniramine (5 mg), and paracetamol (1000 mg) were administered. The patient recovered slowly over 12 hours. Her symptoms had disappeared completely after 24 hours, and she was discharged.

Discussion

Ibuprofen is the NSAID most frequently involved in DIAM [2,3]; however, diagnosis of this condition is challenging [3-9]. During the first 2 admissions of our patient, we could not identify an infectious agent and had to perform a drug challenge to confirm the diagnosis. Quick resolution of symptoms distinguishes DIAM from viral meningitis, in which recovery usually takes 10 to 14 days. The diagnosis of DIAM is made by establishing a temporal relationship with the administration of the drug, onset of clinical symptoms, and rapid resolution after withdrawal. The marked hypersensitivity experienced by our patient, who suffered severe and immediate symptoms with a single dose of ibuprofen, is noteworthy.

Our findings strongly suggest that the term meningoencephalitis is more appropriate in view of the presence of confusion, unresponsiveness, psychomotor slowness, and cognitive disturbances in the second episode. Although uncommon in DIAM, encephalitis has been reported [4,5,9].

Also noteworthy in the present case is the absence of underlying conditions such as HIV infection, systemic lupus erythematosus (the most frequent underlying condition associated with DIAM) [3,5], or other connective tissue disease [2,3]. The history of a good response to breast cancer is remarkable. We could speculate on the influence of previous breast cancer treatment (chemotherapy) or other oncologic treatment (eg, opioids and corticosteroids), as both could have affected the immune system; however, the patient had been in remission for 3 years.

Most episodes of ibuprofen-induced aseptic meningitis consist of an acute meningeal syndrome with a predominance of neutrophils in CSF (72.2% of episodes) and elevated protein

in CSF [5]; consequently, the clinical presentation of this type of aseptic meningitis may be quite similar to that of acute bacterial meningitis. CSF glucose levels are usually normal, and this may help to differentiate between these 2 types of meningitis. Our patient showed normal glucose values and a high protein level in all the CSF analyses. Neutrophilic pleocytosis was present in the first episode and predominant lymphocytosis in the second and third episodes. Differences in lumbar puncture findings could be because the procedure was performed at different times, corresponding with different stages of the disease. These observations might help to clarify the pathogenesis of DIAM, which is not well understood. Prior exposure to the drug, more severe symptoms on re-exposure, cellular changes in CSF, and resolution of symptoms following discontinuation of the drug are all suggestive of a hypersensitivity reaction, the most likely of which are type III and type IV. Skin testing with ibuprofen was negative in our case. Like other authors, we did not find any evidence of type I or type III reactions [6]. It has been suggested that the drug combines with a CSF protein that acts as a hapten, thus explaining the restricted localization of the inflammatory response to the meningeal compartment [7].

Reactions have been reported to arylpropionic acid derivatives [8,9] and several unrelated NSAIDs [10]. In our case, acetylsalicylic acid and paracetamol were well tolerated, and all arylpropionic acid derivatives and arylacetic acid derivatives were forbidden. Ashwath and Katner [10] described a case of DIAM due to naproxen, ibuprofen, and rofecoxib in a single patient. Drug challenges were not performed. It is difficult to identify a specific mechanism in this case, because rofecoxib is not an arylpropionic acid derivative, but belongs to the cyclo-oxygenase II inhibitor class. A drug challenge with rofecoxib could have clarified the presence of cross-reactivity.

Drug challenge may be necessary to determine what advice we should give our patients. Moreover, the contradictory CSF results in 2 admissions in our patient made drug challenge necessary. Nevertheless, risks are present, especially if the patient is taking several drugs or drugs used to treat other diseases or if the patient has atypical findings in the meningeal syndrome.

In summary, NSAID-induced aseptic meningoencephalitis is a rare occurrence, but it is important for physicians to be aware of this dramatic adverse effect of such a widely prescribed medication.

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