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Dual drug-induced aseptic meningoencephalitis: More than a suggestion

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Abstract

We present the case of a patient with a first single episode of a dual drug-induced aseptic mening (DIAM) due to amoxicillin and ibuprofen and a short review of updated literature. A 76-year-old man was admitted to our hospital with slowness and confusion following a dental and gingival inflammation treated with oral amoxicillin 500 mg bid and ibuprofen 600 mg tid for 1 week. His mental state and higher functions abruptly worsened after therapy increase leading to hospitalization. Both the drugs were stopped and the patient improved rapidly within 2–3 days and was released asymptomatic after a week. On the basis of this temporal relationship with a comprehensive negative neuroimaging and laboratory testing for viral, bacterial, and mycobacterial micro-organisms, a DIAM by amoxicillin and ibuprofen was diagnosed. We support the hypothesis that this dual therapy was causative because of the progressive onset of central nervous system symptoms starting at a low amoxicillin dose with a high ibuprofen intake and that this sort of chemical meningoencephalitis was mostly due to the pharmacokinetic of amoxicillin after its dose increase. To our knowledge, this is the first documented publication of a severe first episode of DIAM with predominant higher function involvement caused by these two drugs commonly used together, amoxicillin and ibuprofen.

Keywords

Amoxicillin, aseptic meningoencephalitis, dental inflammation therapy, dentistry, drug toxicity, ibuprofen, neurology

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Introduction

Drug-induced aseptic meningitis (DIAM) is a rare cause of adverse reaction to drug therapy. It is a rare idiosyncratic event which may occur after local or systemic drug administration and in which any other causes of meningoencephalitis were ruled out. Moreover, DIAM is a relatively uncommon and probably underestimated diagnosis, and only about 200 cases have been reported in the literature so far.[1] Clinical picture of DIAM can mimic a viral subacute infection and includes meningeal (headache, neck stiffness, Kernig and Brudzinski signs) and brain damage symptoms (slowness, somnolence, seizures) with a marked predominance of the former ones as reported in the literature. Fever, if present, is usually mild and inflammatory indexes as C reactive protein (CRP) are low. Many kinds of drugs are involved in DIAM and their number is continuously increasing. The most commonly involved drugs are nonsteroidal anti-inflammatory drugs (NSAID) as ibuprofen[2] which is a non-selective inhibitor of cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2). Pharmacokinetic properties of ibuprofen, especially its short plasma half-life of elimination and the lack of development of pathologically related metabolites, are in support for the view that these pharmacokinetic and notably metabolic effects of ibuprofen favour its low toxic potential. Nevertheless, ibuprofen at high doses can exert its toxicity on various cellular processes that are affected by the inhibition of the COX pathway or can act as a hapten with tissue proteins and cause a local inflammatory process. Other frequently reported offending therapies include many antimicrobials, such as co-trimoxazole, trimethoprim-sulfamethoxazole, metronidazole and isoniazid and the antibiotic compounds ciprofloxacin and cephalexin among cephalosporins and amoxicillin among penicillines.[3,4] Amoxicillin has been in use since the 1970s; it is the most widely used

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penicillin both alone and in combination with the beta lactamase inhibitor clavulanic acid, and it is a mid-spectrum, bacteriolytic, β-lactam antibiotic commonly used to treat dental and upper airways infections.[5] It is commonly chosen among β-lactam antibiotics of this class because it is absorbed very well, after oral administration.[5] Finally also allopurinol, ranitidine, carbamazepine, vaccines, monoclonal antibodies against the T3 receptor and, pan T-cell antibodies and even intravenous immunoglobulin and radiographic agents have sometimes been implicated in causing DIAM.[3]

Case report

A 76-year-old man with a negative history of any allergies or auto immune pathology started amoxicillin 500 mg bid and ibuprofen at high dose 600 mg tid for an aching dental and gingival infection with no detectable local abscess with fever; after 5–7 days he started feeling dizzy and then was suffering from somnolence, amnesia, ideative and perceptive slowing and was admitted to the hospital emergency room (ER). Blood values were normal at admittance and did not change during the time spent in hospital (creatinine = 1.16 mg/dL, glomerular filtration rate = 71 mL/min, aspartate transaminase = 20 U/L, alanine transaminase = 20 U/L) except C-reactive protein = 6.7 mg/L, white blood cell = 12.07 × 10E3 c/μL with neutrophils 9.36 × 10E3 c/μL. Computed tomographic scan of the brain was normal. Based on an oral inflammation clinical picture, amoxicillin was increased to 1 g tid, clavulanic acid was added and the patient was released. The next day his clinical picture worsened abruptly leading to a severe higher brain functions impairment with apraxia, mental slowing and marked somnolence with profound asthenia and hyporexia. Absent were clear meningitis symptoms (headache, meningism, stiffness) while a subtle myalgia was later reported during hospitalization. The patient was then admitted to ER with blood values similar to the day before and his neurological picture was unremarkable, with no headache or meningism. Also fever, seizures, myoclonus, ataxia and psychosis were absent. Cerebrospinal fluid (CSF) showed mononuclear pleocytosis (96/mm^3), a normal glucose level and elevated protein concentration (82 mg/dL). CSF routine cultures and a full viral screening with multiplex polymerase chain reaction (PCR) assay for conventional meningoencephalitis from primary CSF cultures (namely *Streptococcus pneumoniae* and *agalactiae, Neisseria meningitidis, Listeria monocytogenes, Haemophilus influenzae, Escherichia coli*, cytomegalovirus, enteroviruses, herpes simplex virus type 1, 2 and 6 and varicella-zoster virus, human parechovirus, *Cryptococcus neoformans*) was negative. No brucellosis or Lyme disease risk was reported. Electroencephalogram (EEG) showed a marked slowing of the basal rhythm with diffuse theta-delta bursts lasting 3–4 s, predominantly rostrally that gradually disappeared in the following days. A brain Gadolinium magnetic resonance imaging (MRI) was normal too. Patient was then treated symptomatically with ceftriaxone 1 g bid for the dental infection and both amoxicillin and ibuprofen were promptly stopped. His symptoms resolved within 72 h after drugs discontinuation with a normalization of CRP value (1.6 mg/L). Prior and during this episode, he did not take any other drug. In the following weeks, CSF cultures were negative and no causative microorganism was identified and patient was free from toothache. At a 9-month follow-up the patient is asymptomatic.

Discussion

Diagnosis of DIAM in our patient was based on published criteria: a temporal relationship with drug intake, CSF pleocytosis, negative extensive microbiological tests, rapid complete resolution after drug discontinuation;[6] positive rechallenge was not present in our case because after the amoxicillin dosage increase clinical picture clearly worsened and led to the suspicion of a drug-related encephalitis. Any concomitant abnormalities in renal or liver function were excluded. Detailed anamnesis is always essential to have a DIAM diagnosis, because it is particularly related to any medication used immediately prior to the appearance of symptoms of central nervous system (CNS) impairment and it is crucial establishing a temporal relationship between the administration of the drug, the onset of clinical symptoms and the rapid resolution of the syndrome after drug withdrawal.[7] As described in the literature, no gender predominance is reported in DIAM, mean age of reported cases is 60 years (29–86) with a latency time ranging from 12 h to 4 days from drug intake and a shorter resolution time in younger subjects but usually seen in 3–4 days. All the patients had CSF pleocytosis, 50% of the cases lymphocytes and 50% mononuclear while the 100% had an elevated protein and normal glucose amount. Of course extensive CSF cultures and viral PCR are negative as necessary criteria for diagnosing DIAM. As for our patient, we believe that both amoxicillin and ibuprofen could have caused our patient's DIAM through a synergic effect of the two drugs because the first CNS symptoms were present with a high ibuprofen and a medium amoxicillin dose even if the marked worsening after the dose increase of amoxicillin makes very probable that the former could be the precipitating factor and most effective drug. Noteworthy in our case is the fact that the predominant clinical deficits were mostly only cortical and they fluctuated in some days from aspecific slowness with somnolence to apathy and ideative apraxia after 10 days at a full amoxicillin dose while meningitis symptoms were always mild and fever absent. Recovery was fully complete after 3–5 days from release and patient blood values prompt long-lasting normalization with CRP value 1.6 mg/L make a false negative CSF culture/PCR very unlikely. Moreover, the patient was on ceftriaxone therapy only a few days after release with no further infection symptoms. Physiopathological mechanisms of DIAM are little known and are partially described. They may be different according to the causing

agent and the situation of every single patient. Two types of mechanisms are commonly proposed for DIAM: a direct chemical irritation of the meninges or a delayed hypersensitivity response while an IgE-mediated mechanism has never been reported.[8] We instead suggest that since amoxicillin absorption rate appears to be saturable, this results in a non-linear increase and a later maximal time for higher doses.[9] Increasing the dose results in a larger percentage of free minimal inhibitory concentration (MIC) due to this delayed absorption, despite the non-proportional increase in maximal concentration. However, a higher dose increases the risk of adverse events, and a shorter interval between doses leads to a larger free MIC as well. The dose/frequency balance should be optimal to get the most antimicrobial efficacy and the lowest risk of adverse events. In fact, DIAM CSF pattern could be related to this pharmacodinamic model. Clinicians should be cautious about prescribing ibuprofen or oral amoxicillin regimens at high doses as well as switching from twice to three times a day and this fits with our patient's clinical course.[10] The absence of evident meningitis symptoms could be due to a minimal or totally absent inflammation of the meninges, as suggested by CSF pattern, with a predominant higher functions imbalance directly related to drugs effect and promptly withdrawing after therapy discontinuance.

Conclusion

DIAM is a rare condition and can be a difficult diagnosis, commonly underrated in polytherapies. A detailed anamnesis, particularly focused on drugs used immediately prior to the onset of CNS impairment, is essential for DIAM diagnosis, even when a number of drugs are prescribed. In all previous literature cases of amoxicillin-related DIAM, a documented positive rechallenge since the first episode of aseptic meningitis is reported, ranging from 2 to 7 episodes, because DIAM was not attributed to amoxicillin at first, as exhaustively reviewed in published papers. Conversely, in our patient the amoxicillin dose increase led to a rapid and marked clinical worsening making rechallenge unnecessary for the diagnosis. We believe that this could be a further strong issue in diagnosing DIAM even at the very first episode. We suggest that non-linear absorption pharmacokinetics of amoxicillin should be kept in mind to avoid serious consequences related to dose regimens and leading to harmful clinical breakpoints mostly when other potentially harmful drugs (ibuprofen and NSAID) which are known to cause DIAM are prescribed together. This could be kept in mind by physicians who often prescribe this kind of medications in their daily practice, dentists and otorhinolaryngologists above all, who daily deal with patients' oral and dental pathologies and inflammatory diseases.

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Ethical approval

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Informed consent

I have obtained the necessary written patient informed consent to publish patient information.

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