

Case Report:

IgE-Mediated Hypersensitivity After Ibuprofen Administration

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Abstract. Although many immunoglobulin-related drug sensitivities have been described, there is a paucity of reports regarding IgE-related drug sensitivities. Here we describe a case of a patient who demonstrated IgE-mediated sensitivity to ibuprofen.

Keywords: aseptic meningitis, hypersensitivity, ibuprofen, serum IgE

Case Report

A 78-yr-old man presented to the emergency room with occipital headache, confusion, drowsiness, and fever of acute onset. These symptoms began 15 min after he had ingested ibuprofen, prescribed to treat arthralgia. The patient had no photophobia but complained of neck stiffness. He had no history of sore throat, cough, shortness of breath, diarrhea, or dysuria. He had a traumatic brain injury 15 yr earlier, due to a car accident. The injury consisted of a small subdural acute hematoma in the left hemisphere, with no skull fracture. At that time he was admitted to a hospital for observation lasting one week. The patient experienced total clinical recovery without medications or surgery.

During the past 5 months, the patient had experienced 3 episodes of meningitis without an identified cause. Various possible causes, such as CSF fistulas, infections, connective tissue disorders, and malignancy had all been investigated and excluded. The patient was taking bisoprolol for cardiac failure. He had no known food or drug allergies; his social history was unremarkable.

On neurological examination the patient was lethargic and was oriented neither to time or place. He had normal language, cranial nerve, and motor functions, but he displayed neck rigidity and bilateral Babinski signs. He was normotensive and febrile. Physical examinations of his other organ systems were normal.

Laboratory tests revealed leukocytosis (13.3×10^3 clls/mm³) with neutrophil predominance and increased concentration of serum C-reactive protein (9.35 mg/dl). An extensive panel of other laboratory tests was unremarkable, except for a highly elevated concentration of serum immunoglobulin E (IgE) of 1099 µg/ml (reference range <170 µg/ml). Urinalysis, blood cultures, and urine cultures were negative. Cerebrospinal fluid (CSF) analysis revealed a normal cell count but elevated protein (0.98 g/L) and glucose levels. CSF cultures grew no organisms. Electrocardiogram showed no acute changes and chest X-ray showed no evidence of an infiltrate. Computed tomogram (CT) and magnetic resonance imaging (MRI) of the head were unremarkable.

The patient's medical records documented that 3 episodes of aseptic meningitis had occurred within the past 5 months. At least 2 of the episodes were associated with ibuprofen ingestion. In the 3 prior episodes of meningitis, serologic tests for

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Lyme disease, herpes, anti-nuclear antibodies, ds-DNA, anti-SSA, anti-SSB, and rheumatoid factor were all negative.

The patient was treated symptomatically during his hospital stay. His mental status and neurologic findings improved within 48 hr and he became afebrile. A subsequent assay of his serum IgE level dropped to normal. The patient was discharged from the hospital with a presumptive diagnosis of aseptic meningitis caused by ibuprofen-induced hypersensitivity. The patient was advised to avoid taking ibuprofen or other nonsteroidal anti-inflammatory drugs (NSAIDs) in the future.

Discussion

Exposures to NSAIDs, particularly ibuprofen, have occasionally been linked to aseptic meningitis. Several case reports exist on this topic [1,2] but few have looked at its association with serum IgE titers. In the present study, upon initial examination our patient had an extremely elevated level of serum IgE. Although the diagnosis of drug-induced aseptic meningitis (DIAM) relies heavily on exclusion criteria [2], the clinical signs and CSF findings may vary [3]. The main categories of causative agents include NSAIDs, antimicrobials, and vaccines [3]. Possible mechanisms have been described for DIAM, including direct irritation of the meninges by intrathecal administration of the drug, and type III or type IV hypersensitivity reactions to the drug [3]. DIAM is treatable by withdrawal of the specific drug in question [3].

In our patient with an extremely elevated serum IgE level, it would have been advisable to check the IgE specificity to ibuprofen by an enzyme linked immunosorbent assay (ELISA). Anania et al [4,5] measured specific IgE levels in cases of drug allergy and found the ELISA test to be a useful aid in confirming the diagnosis. Another confirmative approach for diagnosis would have been an oral challenge, but unfortunately the patient was lost to follow-up. Serum IgE levels had not been measured during our patient's prior episodes of aseptic meningitis. Nonetheless, in light of the 3 episodes of aseptic meningitis that occurred following ibuprofen administration, we speculate that our patient had DIAM.

Our patient did not display CSF pleocytosis, often described with neutrophil predominance in patients with DIAM, but he did have an elevated CSF protein level and negative cultures, which are also commonly observed [6]. Ibuprofen-induced meningitis is most often seen in patients with systemic lupus erythematosus (SLE), Sjogren's syndrome, and mixed connective tissue diseases, although reports in previously healthy individuals have also been published [1,7,8]. SLE, an autoimmune disease characterized by the production of pathogenic autoantibodies to nucleoproteins and DNA, may be caused by anti-DNA antibodies and deposition of these immune complexes in the kidneys [9]. Toll-like receptors, cytokines, and Fc receptors expressed by plasmacytoid dendritic cells may also play a role in the pathogenesis of SLE [9]. Patients with mixed connective tissue disease, as well as those with SLE, may be at risk for developing reactions to ibuprofen [7].

The mechanism of NSAID-induced aseptic meningitis has not been definitely established. However, several mediators of inflammation and immediate hypersensitivity (type I response) have been implicated in neurologic diseases [10]. Evidence corroborating this theory is that (a) the symptoms are not dose-dependent, (b) the rapidity of symptoms increases on subsequent re-exposure, and (c) the symptoms resolve upon discontinuation of the agent, as seen in our patient. Although the cardinal signs of an allergic reaction were absent in our patient, facial edema and/or conjunctivitis have been reported in 25% and rash in 22% of patients with NSAID-induced aseptic meningitis [11].

Although IgE responses that are manifested as neurological reactions to NSAIDs have not been reported, there have been reports of other systemic manifestations, including cutaneous, respiratory, and anaphylactoid reactions [12-14]. Furthermore, the possible presence of an IgE-mediated allergic response to ibuprofen poses another mechanism for drug-induced meningitis. Elevated levels of IgE have been described in neurologic diseases including neurofibromatosis [15], stiff person syndrome [16], tuberculous meningitis [17], and meningoencephalitis due to *Angiostrongylus cantonensis* [18]. Meningitis has also been reported as an uncommon complication of hyper-IgE syndrome [19,20],

suggesting a possible relationship that warrants further evaluation. Garty et al [21] reported that patients with hyper-IgE syndrome have an increased risk of opportunistic fungal infections such as cryptococcal meningitis.

Antigen-specific IgE has been shown to be a mechanism of anaphylaxis in an animal model of multiple sclerosis [22] and in a systemic anaphylactic reaction to glatiramer acetate (GA), with the presence of IgE anti-GA antibodies [23]. In humans, there appears to be an association between ibuprofen-DIAM and diseases of the connective tissue, such as systemic lupus erythematosus [3]. IgE-mediated mechanisms have been associated with other diseases of the CNS, such as Parkinson's disease [24]. Hunot et al [24] reported that Fc epsilon RII/CD23 is expressed in both astroglial and microglial cells of Parkinsonian patients and is not detectable in control subjects.

It is possible that our patient had an underlying undiagnosed immune dyscrasia. In that case, it might be that IgE production was a byproduct of improper antigen processing or a reaction to ibuprofen as a superantigen. Superantigens are considered to exacerbate autoimmune inflammation through expansion of autoreactive T cells [25]. An immune response to staphylococcal superantigens in myelitic patients with atopic diathesis and elevated IgE levels has been reported [25].

Another mechanism by which elevated IgE levels associated with ibuprofen administration might cause aseptic meningitis is molecular mimicry. Molecular mimicry has been proposed as a hypothesis to explain the pathogenesis of multiple sclerosis [26]. Molecular mimicry occurs when peptides from pathogens share sequence or structural similarities with self-antigens [26]. In our patient, exposure to some pathogen for meningitis and/or IgE antibodies might mimic a specific CNS antigen, leading to initiation of disease when later challenged by a nonspecific trigger (ibuprofen). However, molecular mimicry alone may not be able to induce disease [26]. It has been reported that antigenic mimicry may be a consequence of paratope-specific modulations and that it is not solely dependent on the properties of the epitope [27].

In summary, we report an unusual case of a patient with a presumptive ibuprofen-induced allergic response that was manifested as meningitis. Ibuprofen seems the main culprit of NSAID-induced aseptic meningitis; however, sulindac, naproxen, and diclofenac are some of the other commonly used agents that have been implicated [28]. A careful history of drug usage should be taken from patients presenting with meningitis, particularly when the cause is unclear and CSF cultures are negative. NSAID-induced aseptic meningitis appears to be rare, but its actual incidence is probably underreported, in view of the large number of people who consume NSAIDs.

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