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CASE REPORT

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Drug induced aseptic meningitis: A diagnostic challenge

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Abstract Drug-induced aseptic meningitis (DIAM) is a rare but important and often challenging diagnosis for the physician. Intake of antimicrobials, steroids, analgesics amongst others has been implicated. Signs and symptoms generally develop within 24-48 hours of drug ingestion. The patient often exhibits the classic symptoms of meningitis.

Aim: Two cases of drug induced meningitis are presented with review of literature.

Case reports:

Case I: A 13 year old male with a three days history of persistent fever, vomiting, abdominal pain and poor appetite. He also had generalized throbbing headache and neck pain of a day's duration. He had been on Bactrim® for urinary tract infection (UTI) three days prior to the onset of the present symptoms.

On examination, he had altered mental status (confused), neck stiffness and a positive Kerning's and Brudzinski's signs. Muscle tone and deep tendon reflexes were normal with no cranial nerve deficits. Other systems examinations were unremarkable.

Case II: 15 year old male with no significant past medical history presented with a day's history of altered mental status, headache with no fever. He had been on self-medication with over the counter Ibuprofen tablets for intractable headache three days prior to presentation. Examination showed equivocal neck stiffness clouded by profound altered mental status. They were both initially managed for meningitis. Cerebrospinal fluid work-up for both cases ruled out infectious etiologies. Possible drug induced meningitis was then considered.

Conclusion: Drug-induced aseptic meningitis is rare but should be considered in the differential diagnosis of patients presenting with acute or recurrent symptoms and signs of meningitis, especially after infectious causes have been ruled out.

Introduction

Drug induced meningitis has been reported following administration of various agents including antimicrobial, cytotoxic and non-steroidal anti-inflammatory drugs; intrathecal steroids and intravenous immune globulins (IVIGs).[1] Antibiotic induced meningitis has been reported mostly with sulphonamides[1]. Symptoms develop a few hours to days after the exposure to the antibiotic and include headache, nausea, myalgia, chills, fever, and confusion[2]. Resolution of symptoms may occur within a few to several days after drug discontinuation. The clinical and cerebrospinal fluid profile (neutrophilic pleocytosis) may not allow DIAM to be distinguished from infectious meningitis[3].

There are no specific characteristics associated with a specific drug- thus posing a diagnostic and management myth. Typical cerebrospinal fluid (CSF) findings consist of polymorphonuclear pleocytosis, normal glucose, and elevated protein[4]. The mechanisms proposed involve either a direct chemical irritation or a hypersensitivity reaction. The benign nature of drug induced meningitis and the progressively shorter time interval between ingestion of the drug and the appearance of symptoms on drug re-exposure suggest that an allergic mechanism is involved[5].

This paper describes two case of DIAM: an antibiotic-Bactrim and a non-steroidal anti-inflammatory agent-Ibuprofen.

Cases and Method

Case I

A thirteen year old male student presented with a three day history of persistent fever, vomiting, abdominal pain and poor appetite. He had generalized throbbing headache and neck pain of a day duration. He had been on prescribed Bactrim® for urinary tract infection (UTI) for about three days prior to the onset of the present symptoms. On examination, the blood pressure was 100/70mmHg, the pulse rate was 113/ minute, temperature of 38.2 ^{o}C, anicteric, altered mental status

(confused, with incoherent speech and impaired orientation), with neck stiffness and a positive Kerning's and Brudzinski signs. He also had a normal tone and deep tendon reflexes. There were no cranial nerve deficits. Chest was clinically clear to auscultation and he had no murmurs. Abdominal and other system examinations were essentially normal.

Laboratory Results

White blood cell count (WBC) was 2 x 10^9/l, haemoglobin / hematocrit (Hgb/Hct) values were 9.5g/dl /30%, Platelets 20 ×10^9/L, Cr 3.6, blood urea nitrogen (BUN) 18mmol/l,sodium (Na) 137mmol/l. Cerebrospinal fluid (CSF): opening pressure 200mm H_2O, gram stain was negative, sugar 30mg/dl, protein 115mg/dl, WBC 125cells/microl and lymphocytosis 80%. CSF: bacterial antigen screen was negative, polymerase chain reaction showed no detection for Cytomegalovirus, Herpes simplex virus I&II, arbovirus panel and Mycobacterium tuberculosis and Ebstein barr virus. CSF and blood cultures yielded no growth after 48 hours and five of days incubation respectively.

Other tests done included: Galactomannan Assay, urine histoplasma antigen, Quantiferon Gold Assay, HIV test which were all negative. Computed tomography scan (CT) and magnetic resonance imaging scan (MRI) of the brain showed no acute lesions.

The child was empirically started on intravenous Rocephin, Vancomycin and Acyclovir pending further evidence of non-infectious etiology. The bactrim was discontinued on admission with serial monitoring of creatinine which trended down to normal prior to discharge. His mental status and neurologic findings improved within 48 hours.

Platelet transfusion was given prior to lumbar puncture to prevent bleeding as quantitative versus qualitative defects could not be ruled out at presentation. The patient was discharged from the hospital with a presumptive diagnosis of aseptic meningitis caused by Bactrim hypersensitivity. The patient was advised to avoid taking bactrim in the future. He has continued to do well on follow up.

Case II

This was a 15 year old male with no significant past medical history who was admitted via the emergency room for evaluation of altered mental status. For the last three days prior to presentation, he had been taking several pills of Ibuprofen for an intractable headache. This was not his first exposure to Ibuprofen. On examination, temperature was 39 ^oC, blood pressure of 110/65 altered mental status, he was talking irrationally, disoriented in time and place, equivocal neck stiffness, Kernig's sign was positive, hypertonia of the lower limbs. The other systems examinations were normal. He was empirically started on intravenous Rocephin and Vancomycin for presumptive bacterial meningitis which were discontinued after 72 hours as there was no evidence of infective etiology.

Laboratory Results

White blood cell count (WBC) was 5.6 x 10^9/l, Hg/ Hct13.9/dl /41%, Platelets 114×10^9/L, Cr 1.6, BUN15mmol/l, Na 137mmol/l. Cerebrospinal fluid (CSF): opening pressure ~ 200mmH_2O, gram stain was negative, sugar 42mg/dl, protein 102mg/dl, WBC 75cells/microL, red blood cell 0-1, lymphocytosis 73%, neutrophils 17%, blood cultures were negative. CSF white cell count was 65 with 75% polymorphs.

CSF: Bacterial detection antigen screen was negative, gram stain showed no organism. Polymerase chain reaction (PCR) showed no detection for cytomegalovirus, herpes simplex virus I&II, Arbovirus panel and Mycobacterium tuberculosis and Ebstein barr virus. Miscellaneous tests such as galactomannan assay, urine histoplasma antigen, Quantiferon Gold Assay, HIV tests were all negative. Computed tomography scan (CT) and MRI of the brain showed no acute brain lesions. Ibuprofen was discontinued and his symptoms resolved within 72 hours of admission with no neurological deficits.

Discussion

The two cases presented here were on drugs namely Bactrim and Ibuprofen respectively. The interval between drug intake and the development of meningitis varies widely. Signs and symptoms usually appear within 24 to 48 hours after drug ingestion, but symptoms may not appear in some cases for up to two years post-therapy.[6] Our patients had symptoms appearing early. This pattern has also been noted and reported previously.[7,8]

Drug-induced aseptic meningitis (DIAM) has been reported as an uncommon adverse reaction to numerous drugs. It is a diagnosis of exclusion, and clinical signs and CSF findings vary greatly[5]. The incidence of drug induced meningitis remains unknown as most cases diagnosed are unreported and many remain unrecognized. The body of evidence regarding DIAM is largely in the form of anecdotal case reports and must be interpreted carefully bearing this in mind[6]. The major categories of causative agents are non-steroidal anti-inflammatory drugs, antimicrobials, intravenous immunoglobulin, intrathecal agents including steroids, vaccines and a number of other less frequently reported agents such as vitamins. Drug induced aseptic meningitis can mimic an infectious process as well as meningitis secondary to systemic disorders for which treatment of these drugs were used. [6,9,10]

Drug-induced aseptic meningitis may develop in a patient who initially was able to tolerate the causative drug. The patients in our report have had previous exposures. Prior exposure to the drug has been noted in 45% of patients taking NSAIDs; and 35% and 3% for antibiotics and IVIGs respectively[2]. These rates of prior exposures are not surprising, considering the inappropriate and high frequency with which NSAIDs and antibiotics are prescribed.

The majority of patients with DIAM, irrespective of the offending drug, present with headache, fever, meningismus and changes in mental status which are also symptoms characteristic of infectious meningitis[3].Therefore, the clinical presentation does not help to differentiate DIAM from infectious meningitis. DIAM is also associated with other systemic diseases. There appears to be an association between DIAM and connective tissue disease, particularly systemic lupus erythematosus and Ibuprofen; migraine has been suggested as a predisposing condition.[4]

There are two major proposed mechanisms for DIAM. The first involves direct irritation of the meninges by intrathecal administration of the drug, and the second involves immunological hypersensitivity to the drug most likely type III and type IV hypersensitivity reactions. The mechanism of action of antibiotic- induced meningitis is due to hypersensitivity reaction just as it is for NSAIDs[2]. Recognition and diagnosis of DIAM is important, as it is treatable by withdrawal of the drug and recurrence is thus prevented. The outcome of DIAM is generally good, usually without long term sequelae [10,11]

The Patients' clinical presentations provide an opportunity to discuss the differential diagnosis of meningitis. Acute Bacterial meningitis is usually of sudden onset and characterized by an appearance of being ill: High fever, Headache, Photophobia, abnormal CSF picture such as predominance of neutrophils, elevated protein and decreased glucose. The predominance of lymphocytes in the CSF and negative cultures makes diagnosis of bacterial meningitis unlikely in both cases. Viral meningitis (VM) though typically diagnosed in young patients, early in its course, there may be prevalence of neutrophils in the CSF with a subsequent shift to lymphocytosis.

Enteroviruses may be isolated by culture or PCR techniques. This test being highly sensitive and specific was negative in both patients. Herpes simplex I/II PCR was also negative. It was concluded that viral encephalitis/ meningitis was ruled out since the viral PCR remained undetected.

Neuroimaging was normal in both cases as well. This is similar to other cases that have been reported previously.[12] However, there are some cases of NSAID – induced DIAM described in literature where diffuse contrast hemispheric enhancement was evident by magnetic resonance imaging and computed tomographic scan probably reflecting a blood-brain barrier breakdown.[9,12]

Conclusion

There should be a high index of suspicion in all patients presenting with symptoms of meningitis with negative CSF culture. Detailed drug history should be obtained including a thorough search for over the counter medications which very often are either ignored or taken for granted both by the physicians and patients.

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