Co-trimoxazole induced aseptic meningitis

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Abstract
A 15 year old boy presented with two episodes of aseptic meningitis-like reactions after ingestion of co-trimoxazole. The diagnosis of co-trimoxazole induced aseptic meningitis was made. This syndrome should be considered in the differential diagnosis of aseptic meningitis.

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Aseptic meningitis is relatively common in childhood and has many causes besides viral infections. In the adult literature there are several case reports of drug induced aseptic meningitis. After an extensive search Maignen et al found 11 cases after ingestion of co-trimoxazole and eight cases after trimethoprim.1 So far we are aware of only one case report of aseptic meningitis after co-trimoxazole in childhood.2 This drug is currently widely used in paediatric practice and therefore to increase

awareness of this potential adverse effect we report another case.

Case report
A 15 year old boy with insulin dependent diabetes mellitus was admitted with fever, headache, and vomiting. Earlier on the same day he had received co-trimoxazole (Septrin, Wellcome) for the first time as treatment for an upper respiratory infection. His symptoms worsened over a few hours and he rapidly became unwell. On examination, his temperature was 38.2°C and he had marked photophobia. He had neck stiffness and Kernig’s sign was strongly positive. His fundi were normal. A lumbar puncture resulted in a traumatic tap and intravenous cefotaxime was begun with the presumptive diagnosis of bacterial meningitis. Computed tomography of the head was normal. He began to improve and was almost back to normal within 48 hours. There was no leucocytosis on peripheral blood film and blood cultures were negative. He was discharged after 10 days of antibiotic treatment.

Three weeks later, he was well when reviewed. However, he was complaining of dysuria and was prescribed co-trimoxazole for mild balanitis. Fifteen minutes after ingestion of the first dose (480 mg) he had fever with rigors, severe headache, and vomiting. On admission to hospital he looked unwell and was febrile (temperature 39.1°C). He had photophobia and meningal signs were strongly positive. Examination of his cerebrospinal fluid showed 122 white blood cells/μl (100% polymorphonuclear leucocytes), protein 1.16 g/l, and a normal glucose concentration. Intravenous antibiotics were started and his symptoms settled within 48 hours.

The following tests on the cerebrospinal fluid were negative: Gram stain; latex agglutination tests for the antigens of Haemophilus influenzae, Neisseria meningitidis, and Streptococcus pneumoniae; mycobacterium polymerase chain reaction; cytospin preparation for malignant cells; cultures for bacteria, viruses, fungi, and tubercle bacilli. Blood tests were as follows: white cell count 4.6×10⁹/l; there was no growth on culture; serum viral and mycoplasma titres not raised; and tests for Coxsackie virus type B IgM and Borrelia burgdorferi IgG were negative. Serum immunoglobulins and complements were normal except for a slightly raised C3 (1.35 g/l, normal range 0.6–1.2 g/l), thought to be due to acute phase reaction. Urine culture was negative and no viruses were isolated from his throat. Chest radiography and repeat computed tomography of the head were normal. Radiography of the skull and spine were also normal with an incidental finding of spina bifida occulta at S1 level.

We diagnosed co-trimoxazole induced aseptic meningitis. Rechallenge was considered unethical and the patient was asked to avoid the drug. He made an uneventful recovery and there has been no recurrence over a one year period.

Discussion
After the second episode of meningitis, an extensive search for infectious agents, immunodeficiency, and possible anatomic defects along the craniospinal axis was negative in our patient. The diagnosis of co-trimoxazole induced aseptic meningitis was based on the close temporal association with ingestion of co-trimoxazole and rapid recovery after withdrawal. Unfortunately we could not obtain cerebrospinal fluid in the first episode of ‘meningitis’ but even normal findings in the cerebrospinal fluid would be compatible with a reaction to co-trimoxazole as a similar neurological illness has been reported after co-trimoxazole with normal findings. However, usually the cerebrospinal fluid picture is abnormal and consists of polymorphonuclear leucocytosis, raised protein concentration, and normal glucose concentrations, which is similar to our findings. Another feature of this condition, also observed by ourselves, is a trend towards increasing severity and rapidity of onset with each successive exposure to the drug.

Aseptic meningitis has been reported in adults after various drugs, for example, ibuprofen, naproxen, co-trimoxazole, trimethoprim, carbanazepine, and azithromycin. Most cases occurred in young women with connective tissue disorders. The mechanism is unknown, most authors favouring an acute hypersensitivity reaction involving the meninges. Reports of meningitis after trimethoprim alone suggest that this drug could be the offending agent in co-trimoxazole.

This condition may be more common than is currently recognised and should be considered in the differential diagnosis of obscure recurrent meningitis or partially treated meningitis in children. A careful drug history may therefore give an important clue to the diagnosis and avoid unnecessary extensive investigations.

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