Tests were not performed during that episode. He could not remember having taken amoxicillin/clavulanic acid before that first occasion. He did not report any accompanying "allergic" signs, such as facial oedema, conjunctivitis, or rash during either of the two episodes, and he had no previous history of allergy or connective tissue disorder.

His neurological status was unremarkable, and in particular there was no neck stiffness. His physical status was also normal except for a body temperature of 38.2°C. Cranial computed tomography revealed no abnormalities. CSF examination showed the following results: leucocyte count 54 cells/µl (82% lymphocytes, 12% monocytes, 4% lymphoid cells, 2% granulocytes); glucose 62 mg/dl (serum 98 mg/dl); protein 94 mg/dl; Q_{Alb} 13.4 (1000 × CSF albumin/serum albumin, normal < 7.4); IgG index 9.38 (1000 × CSF IgG/serum IgG); oligoclonal bands negative. Bacterial and fungal cultures from CSF were negative. Blood analyses were also normal except for a slightly raised C reactive protein (1.1 mg/dl, normal < 0.5 mg/dl). Additional investigations did not support an underlying type 1 or type 3 hypersensitivity mechanism, as no specific IgE to amoxicillin (< 0.35 IU/ml) or immune complexes interacting with C1q (< 20 IE/ml) were detected in his serum or CSF. Without further treatment, he recovered completely within one week.

Comment

On the basis of the history and findings (two identical episodes of high fever and headache shortly after intake of the prophylactic antibiotic, and sterile CSF pleocytosis at least during the second episode), we diagnosed probable amoxicillin/clavulanic acid induced aseptic meningitis. However, we could not find any evidence suggesting an underlying type 1 or type 3 hypersensitivity reaction. Further studies are therefore warranted.

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Another adverse effect of aspirin: bilateral vestibulopathy

Widely used for more than 2000 years, salicylic acid has numerous beneficial effects. It may also lead to several adverse reactions, affecting for instance the auditory system.[1] Persistent dysfunction of the vestibular system, however, has not yet been described. We report a patient who took 5–6 g aspirin a day for three days for arthralgia. Subsequently he felt unsteady and had oscillopsia while walking, but no tinnitus or hypacusis. Caloric irrigation revealed a bilateral vestibulopathy which was most probably caused by the direct effect of aspirin on the vestibular hair cells.

Case report

A 61 year old teacher took 5–6 g aspirin a day for three days to treat his arthralgia, but no other drugs during this period. Two or three days later he felt unsteady while walking. This problem was worse on uneven ground and in the dark. During head movements and while walking he perceived apparent motion of the visual scene and his vision was blurred. Hearing was normal and he did not complain of tinnitus. He had not had vertigo or hearing problems previously, and his family history was also unremarkable. Though he had had monoclonal (IgG lambda) gammopathy for five years, a bone marrow biopsy proved normal, and thus his condition had been diagnosed as "monoclonal gammopathy of unknown significance."

As all his symptoms persisted, he came to our dizziness unit nine months later. The Halmagyi–Curthoys test (head impulse test to evaluate the function of the semicircular canals) was pathological and revealed a dynamic deficit of the horizontal semicircular canal bilaterally. Romberg testing showed increased sway which worsened when the eyes were closed. His gait was broad based and also worsened with the eyes closed. However, his hearing was normal, and he had no cerebellar signs.

Electronystagmography revealed a significant bilateral caloric hyporesponsiveness (peak slow–phase velocity of the caloric nystagmus during irrigation with 44°C warm water: right ear, 2°/s; left ear, 5°/s; and with 30°C cold water: right ear, 5°/s; left ear, 5°/s). Further, the pre- and postrotatory nystagmus lasted less than three seconds and showed a gain of < 0.2. Hearing tests, including an audiogram, were normal. Blood tests for other possible causes of bilateral vestibulopathy (antibodies against inner ear structures, antinuclear antibodies, anticytoplasmic antibodies, rheumatic factor, vitamin B-12, folic acid, and so on[2]), as well as high resolution magnetic resonance imaging of the cerebellopontine angle and labyrinth were normal. As mentioned above, testing of the serum revealed the presence of monoclonal IgG-lambda gammopathy (total protein 8.7 g/dl (normal range 6.0 to 8.0 g/dl); IgG concentration 28.2 g/l (normal range 7.0 to 16.0 g/l)).

Comment

Pathophysiologically, the patient's complaints are fully explained by bilateral vestibulopathy: the oscillopsia is caused by a defect of the vestibulo-ocular reflex, and the unsteadiness by a defect of the vestibulospinal reflexes, especially in darkness when vision cannot substitute for absent vestibular function. The time course of symptom development following the ingestion of a high dose of aspirin provides strong evidence that the isolated and persistent bilateral vestibulopathy was caused by the drug. Although aspirin induced bilateral vestibulopathy has not been reported before, it is likely that other patients taking aspirin have developed it, as bilateral vestibulopathy is often overlooked.

For more than 150 years it has been known that high doses of salicylates can cause tinnitus, loss of absolute acoustic sensitivity, and alterations of perceived sounds, which may develop in the initial days of treatment.[1] It is also known that the susceptibility of individual subjects to salicylate induced inner ear toxicity varies greatly, but why this is so is unclear. Various attempts have been made to explain the toxic effects of salicylic acid. Otoacoustic emissions have been used to show that salicylates cause changes in the mechanosensory functioning of the cochlea; in particular, spontaneous emissions are decreased.[3] Histopathological animal studies have revealed significant changes of only the outer hair cell lateral membrane. In vitro experiments have shown that the fast motile responses of outer hair cells are reduced. As regards the underlying mechanisms, aspirin seems to directly inhibit the mechanoelectrical transduction process by partitioning the salicylate molecules in the membrane of hair cells.[4 5] These latter findings suggest to us that this newly described adverse reaction to aspirin may be related to our patient's monoclonal IgG-lambda gammopathy. The raised IgG concentration could have promoted such partitioning of the molecules in the hair cell membrane, assuming they are able to enter the endolymphatic space. However, this does not explain the isolated impairment of the vestibular function.

From a clinical point of view, it is relevant to consider this additional adverse effect of aspirin, especially as it is unpredictable owing to varying individual susceptibilities. If a patient has taken higher dosages of aspirin and complains of dizziness, his vestibular function should be tested for bilateral vestibulopathy.

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