A 44 year old woman was admitted to our clinic because of progressive multiple sclerosis. One year before admission she had developed paresis of the legs, and subsequently of the arms. She became incontinent for urine and feces. She also complained of numb feelings and muscle cramps in her legs. The medical history mentioned hypertension for which she used propranolol and hydrochlorothiazide. The family history was negative for multiple sclerosis. On examination there was vertical nystagmus, slight paresis of the arms and legs, incoordination of the arms, and loss of sensation from a mid-thoracic level. The tendon reflexes of the legs were very brisk, and both plantar responses were extensor. Examination of CSF showed eight white cells/mm³ (all lymphocytes), and an intrathecal production of IgG and IgM. Brain MRI and the cervical part of the spinal cord showed multiple white matter lesions. Additional investigations excluded other diseases—for example, borreliosis and lupus erythematosus. A 10 day treatment with daily administration of 1000 mg dose of intravenous methylprednisolone was started. Methylprednisolone was given in its injectable form, methylprednisolone sodium succinate, which hydrolyses to methylprednisolone in the body. The infusion period was one hour. Because of cystitis she received trimethoprim. One day after the infusion the patient developed dyspnea. To guarantee minimal risk, we gave 1000 mg intravenous methylprednisolone under close monitoring. After the first infusion there was a reactivation of the skin rash, and difficulty with swallowing and breathing, suspicious of an anaphylactic reaction. The patient was given intravenously, after which the symptoms immediately resolved. Because of clinical improvement, therapy was continued with a 1000 mg dose of intravenous methylprednisolone divided into two, again under close monitoring. No symptoms developed. The next day we gave the full dose after which the patient developed dyspnea. We waited two days and reintroduced intravenous methylprednisolone therapy in divided doses. After the second dose the patient again became short of breath, needing 4.0 mg intravenous clemastine. We decided to give the patient the next two doses of 500 mg intravenous methylprednisolone followed by 4.0 mg intravenous clemastine, and no symptoms developed.

A skin reaction and histamine release test were performed to elucidate the pathogenesis of the symptoms. The patient showed a skin reaction of 5.5 mm after subcutaneous injection of methylprednisolone (1.0 ml 5% methylprednisolone in isotonic saline). However, when the same solution was subcutaneously injected in nine healthy volunteers, skin reactions of less than 7 mm diameter of 8 mm, ranging from 5.5 to 11.5 mm. To determine if the patient's adverse reactions to methylprednisolone were IgE mediated, a blood sample was drawn and depleted of erythrocytes. This preparation was used for histamine release testing, according to the procedure described by Lichtenstein and Osler. A large amount of methylprednisolone (more than 250 μg/test) resulted in basophilic histamine release. However, this positive result was also found when leukocytes from two healthy donors were used.

To determine whether high plasma concentrations of methylprednisolone might explain the reactions found, we measured blood samples which had been drawn during a day of intravenous methylprednisolone treatment. Reversed phase high performance liquid chromatography was used for the analysis of methylprednisolone and methylprednisolone sodium succinate. Methylprednisolone sodium succinate declined with a half life of 20 minutes leading to methylprednisolone concentrations not exceeding 6.5 mg/l, which is less than those measured in patients receiving high dose intravenous methylprednisolone with no adverse reactions. Reviewing the literature we found only one case report of a patient with multiple sclerosis who developed an anaphylactoid reaction to intravenous methylprednisolone. This patient had a positive skin test for methylprednisolone, and a radio allergosorbent test (RAST) for IgE antibodies was positive. No information regarding the RAST procedure was mentioned.

Mild reactions to oral or intravenously administered corticosteroids in patients have been found but occur infrequently (0.3% of the patients). Risk factors for developing allergic reactions after receiving intravenous methylprednisolone are asthma and aspirin intolerance. Our patient had no history of asthma or other allergies.

Skin tests have been used to investigate the nature of side effects to intravenous methylprednisolone. We showed that skin tests are unreliable as they also gave positive reactions in the healthy volunteers. The "allergic" reactions are probably not based on IgE antibodies, but could have been caused by fast administration of methylprednisolone leading to high plasma concentrations. However, raised concentrations were not found. The histamine release reaction for methylprednisolone sodium succinate was not indicative of an IgE mediated reaction because the concentration of methylprednisolone leading to a (dose related) toxic effect of methylprednisolone on the basophil granulocytes. In conclusion, the clinical symptoms which developed during high dose intravenous methylprednisolone are rare, but can be dangerous. Therefore, patients with multiple sclerosis who receive an intravenous methylprednisolone treatment for the first time should be carefully monitored. According to this case the mechanism of the reaction seems to be IgE independent, and may have been induced by toxic concentrations of methylprednisolone on the basophil granulocytes. Skin testing with methylprednisolone is unreliable, and should be interpreted with care.
Unilateral auditory hallucinations: ear or brain?

Bräsi and Perry convincingly describe a boy with unilateral otopathic auditory hallucinations. However, their literature review is very much focused on CNS causes for auditory hallucinations other than from a hyperactive ear. They also do not cite a relevant prior case.

Paper starts: "Unilateral auditory hallucinations...are associated with contralateral CNS lesions." Their only supporting reference is to the previous review of four adults with neurological disease and unilateral auditory hallucinations, allegedly of cortical origin. These turned out to be anything but. One case (Regis, 1881) had voices in his ears or hearing; his 1892 case, also an alcoholic wine merchant, heard voices in her ears with relatively normal hearing. Whatever other lesions these patients had, there were peripheral lesions sufficient to trigger tinnitus and auditory hallucinations, although in alcoholic patients these can probably be triggered from ears with relatively normal hearing. By contrast with these totally unconvincing cases of non-otological cortical origin, Toulouse reviewed seven cases of unilateral auditory hallucinations from homolateral ear disease, four of which were particularly convincing as the auditory hallucinations vanished (three cases) or waned (one case) with effective ear treatment. Toulouse also noted cases with quite different auditory hallucinations in opposite ears simultaneously if of cortical origin, a quite implausible degree of functional hemispheric independence is shown.

Their next three references supposedly show that auditory hallucinations are caused by stimuli, phenomena in the CNS—namely, epilepsy (Keshavan et al, 1992), schizophrenia (Silbersweig et al, 1995), and drugs (Ketter et al, 1996).

Keshavan et al reviewed musical hallucinations. In epilepsy, they reviewed six cases from Hécaen and Yvert in whom music occurred as part of an epileptic aura, four of whom had concomitant ear disease; three case reports without structural brain lesions, two with pronounced deafness, the third with attacks of nausea and rotary vertigo but no otological investigations; and their Polフィリッド's case of musical hallucinations but no ear or hearing examination. In one of these last three, seizures were of a "new and curious type", including deafness, unilateral voices, and music, starting two years after tumour removal. Far from implicating the brain, this review of musical hallucinations strongly implicates the ear. Even if epileptic patients are not known to have ear disease, this should be suspected, as Jackson and Gowers established last century that epilepsy can arise from the ear.

In their PET study on hallucinating schizophrenic patients, Silbersweig et al found increased blood flow in the thalamus from the ear. They reviewed some of this literature concluding that auditory hallucinations are generated in the brain; instead, it is consistent with peripheral impulses funnelling up via the thalamus.

The volunteers of Ketter et al "consistently (29 out of 32 subjects) reported procaine induced auditory hallucinations (unformed buzzing, ringing, or electronic sounds)." They considered procaine a selective limbic activator, even though no change in cerebral blood flow corresponded to the "auditory hallucinations". In an ear, nose, and throat clinic the above noises would definitely be labelled tinnitus, and an obvious peripheral cause usually found. In line with Gordon's studies, procaine causes cochlear hyperactivation (increased wave I and II amplitude in dogs); in view of the link between epilepsy and the ear, it is noteworthy that the EEG changed from an awake pattern to seizure activity.

The 1986 review of sensory deprivation by Perella et al was cited as an example of auditory hallucinations from sensory disinhibition. I reviewed some of this literature, concluding that for musical hallucinations there is as much evidence for ear disease and labyrinthine hyperactivity as when they occur in all other conditions and diseases. Deprivation is a powerful stimulus; if there is no internal noise, white noise is used to mask environmental sounds, whereas if all background noises are reduced, normal subjects will start to have tinnitus. I recently tested a 16 year old dyslexic patient who had never known silence ("there was always a permanent noise running through it", I think); he had never complained of tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted! A similar case to that of Bräsi and Perry throws considerable light on pathophysiologica processes involved. Both were tormented by voices of devils, having symptoms of unilateral ear disease; saw nothing, not even each other; their voices and mental processing; there were no flickerings or flashes; there was no original tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted!

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