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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 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 hands she had difficulty in coordination 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 immunohistochemical 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, borborexia and lupus erythematosus. A 10 day treatment with daily administration of 1000 mg intravenous methylprednisolone was started. Methylprednisolone was given in its injectable form, methylprednisolone sodium succinate, which hydrolyzes to methylprednisolone in the body. The infusion period was one hour. Because of cystitis she waited two days and reintroduced 1000 mg intravenous methylprednisolone followed by 4.0 mg intravenous clemastine, and no side effects were observed. After informed consent of the patient it was decided to give the patient the next two doses of 500 mg intravenous methylprednisolone divided doses. After the second dose the patient developed urticaria which disappeared after a few days, and which could have been induced by either drug. After informed consent of the patient it was decided to give another course, as the intravenous methylprednisolone course improved her multiple sclerosis. 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 anaphylaxis. The patient was put on a high dose intravenous methylprednisolone treatment. To determine whether high plasma concentrations of methylprednisolone might explain the reactions found, we measured blood concentrations which had been taken 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. 

We reviewed the literature and 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 IgE mediated. The IgE mediated reaction 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. This test also gave positive results due 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?

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 They also do not cite a relevant prior case.

Their paper starts: “Unilateral auditory hallucinations...are associated with contralateral CNS lesions”. Their only supporting reference is a review of seven cases of unilateral auditory hallucinations, allegedly of cortical origin. These turned out to be anything but cortical. The 1888 case, also an alcohol addicted patient, had 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 1968 review of sensory deprivation by Petrella et al was cited as an example of auditory hallucinations from sensory dis inhibition. I reviewed some of this literature, concluding that for musical hallucinations there is as much evidence for ear disease and labyrinthic hyperactivity as when they occur in all other conditions and diseases. Deprivation is a misleading concept; it is the small numbers of 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 dextral patient who had never known silence (“like being deaf has a permanent noise running through it”), yet he had no evidence of tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted!

A similar case to that of Bräsig and Perry throws considerable light on pathophysiologi cal processes involved. Both were tormented by voices of devils having symptoms of unilateral ear disease; saw devils, heard buzzing, thundering, cracking, thumps, etc. Once, he had a musical hallucination (bells of specific church bell) that made him wake in bed because of noises in his head. Curiously, Luther did not have a simple demonic or religious explanation for his torments. Instead he blamed Satan for his Meniere’s symptoms (headache, episodic vertigo, tinnitus), which in turn he recognised caused his hallucinations. In fact his symptoms were typical of profound illness, and it is not surprising that he had "French disease.”

If Bräsig and Perry still assert a CNS origin for auditory hallucinations they need an original case report, not reviews or secondary sources. Repeated appeals for non-otological neurological musical hallucinations have failed (suggested cases with brainstem lesions were also deaf). I would now like to broaden the challenge to cover auditory hallucinations as well. Unless someone can come up quickly with a case of auditory hallucination due to a clear neurological lesion in someone with normal ears and hearing, the only proved cause of auditory hallucinations is otological.

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Bräsig and Perry reply: Gordon conjectures that otopathological physiology is the necessary and sufficient condition for auditory hallucinations. We disagree. We hypothesise that auditory hallucinations have many aetiologies that have not been classified as otological, neurological, neuropsychiatric, and combined. Auditory hallucinations may result from the multiple effects of otopathology, such as altered signal transduction in hair cells. For example, in response to minimal environmental stimuli, damaged hair cells may generate high frequencies producing white noise perceived as tinnitus in some persons. Auditory hallucinations may also result from neurological illnesses, including after right temporal lobectomy for intractable epilepsy. Therefore, auditory hallucinations in neurological disorders are studied, particularly in schizophrenia. On functional MRI, two patients with schizophrenia experiencing auditory hallucinations showed reduced responses of the temporal cortex to external auditory stimulation. Therefore, auditory hallucinations in some patients with schizophrenia may correspond with minimal activation of the auditory association cortex. The physiology of thinking in words was assessed utilising PET in six persons with schizophrenia who experienced auditory hallucinations, six persons with schizophrenia.