This is the first demonstration of neuromyotonia in a genetically engineered animal model of a hereditary neuropathy with a defined gene defect. Our findings may eventually help to define the pathogenesis and mode of treatment of hereditary forms of human neuromyotonia.

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We were supported by a grant from the Swiss National Science Foundation and KVT and JZ by the National Science Foundation and KVT and JZ by the US government. A 44-year-old woman was admitted to our clinic because of progressive multiple sclerosis. One year before admission she had developed paraparesis of the legs, and subsequently of the arms. She became incontinent for urine and feces, and 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 legs, hyporeflexia, 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 immunological 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, borboreusis 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 received trimethoprim. One day after the intravenous methylprednisolone course had ended, the patient developed generalised 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 angioedema. We gave methylprednisolone 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 methylprednisolone after which the patient developed dyspnoea. 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 theophylline. We decided to give the patient the next two doses of 500 mg intravenous methylprednisolone followed by 4.0 mg intravenous theophylline, and no symptoms developed.

A skin reaction and histamine release test were performed to elucidate the pathogenesis of the adverse reactions. We used 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 occurred only at a concentration of 8 mm, ranging from 5.5 to 11.5 mm.

To determine if the patient's adverse reactions to intravenous 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 Oster. A large amount of methylprednisolone (more than 250 μg/test) resulted in basophilic histamine release. However, this positive result was also found when leucocytes 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 obtained 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.

Non-specific 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 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, but rather 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.
CORRESPONDENCE

Unilateral auditory hallucinations: ear or brain?

Brasit and Perry convincingly describe a boy with unilateral otopathic auditory hallucinations. However, their literature review is very much confined to 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 references were to Toulouse’s 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 left ear agitated by alcohol, sounds of a bell and water in his right; impaired hearing in his left ear (though by Toulouse to be of cortical origin!); the 1888 case had bilateral auditory hallucinations, worse on the left, abolished by blocking off the ear which was full of pus; the 1890 case, an alcoholic wine merchant, had bilateral noises (bells, whistles, rattles, etc) which alternated and changed into voices in his right ear, but there was no examination of his ears or hearing; his 1892 case, also an alcoholic wine merchant, heard voices in her left ear, and had bilateral deafness from chronic otitis media. Whatever other lesions these four 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 stimulatory 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 describe six cases from Heinzen who reported 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; the case of Penfield’s cotton brain ball continued 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 implies 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 to the thalamus and not the neocortex. This is not evidence 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 (unusual 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 Paisley’s hypothesis that cochlear hyperactivation (increased wave I and II amplitude in dogs)3; 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 1998 review of sensory deprivation by Petrella et al was cited as an example of auditory hallucinations from sensory disinherit. 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. Depreression is a non-naturalizadosocial condition in which 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 (“became rusted” had a permanent noise running through it“), yet who was not even conscious of tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted!1 A similar case to that of Brasit and Perry throws considerable light on pathophysiological processes involved. Both were tormented by voices of devils commenting on the minor symptoms of unilateral ear disease; saw hallucinations as premonitory signs of coming hearing loss (drowning) of which they were aware and did not want to be aware; they were left in a state of uncertainty and were not in a state of auditory hallucinations. Fortunately, the other case was Martin Luther,1 who clearly described ringing in his ears, unendurable buzzing, thundering, cracks, thumps, etc. Once, he had a musical hallucination (bells of specific church bells) which woke him in bed because of noises in his head. Curiously, Luther did not have a simple demonic or rational explanation for his torments. Instead he blamed Satan for his Meniere’s symptoms (headache, episodic vertigo, tinnitus), in which he recognised caused his hallucinations. In fact his symptoms were typical of meningiitis, which I believe is good evidence that he had “French disease“.

If Brasit 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 brain lesions were also dement). 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 otorological.

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2 Gordon AG. Do musical hallucinations have a neurological cause? J Neurol Neurosurg Psychiatry 1995;59:763-5.

Brasit and Perry reply: Gordon conjectures that otorological pathology is the necessary and sufficient condition for auditory hallucinations. We disagree. We hypothesise that auditory hallucinations have many aetiologies. They can be classified as otorological, neurological, neuropsychiatric, and combined. Auditory hallucinations may result from the multiple effects of otopathological, such as altered signal transduction in hair cells. For example, in response to minimal environmental stimuli, diseased cochlear hair cells respond with different frequencies producing white noise perceived as tinnitus in some persons. Auditory hallucinations may also result from neurological illnesses, including after right temporal lobectomy for intracerebral hemorrhage without seizures. We are preparing a manuscript comparing auditory hallucinations in neurological disorders. Auditory hallucinations due to neuropsychiatric disorders are being studied, particularly in schizophrenia. On functional MRI, two patients with schizophrenia experiencing auditory hallucinations showed decreased responses of the temporal cortex to external auditory stimulation. Therefore, auditory hallucinations in some patients with schizophrenia may correspond with maximal activation of the auditory association cortex. The physiology of thinking in words was assessed utilizing PET in six persons with schizophrenia who experienced auditory hallucinations, six persons with schizophrenia...