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

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KLAUS V TOYKA
JÜRGEN ZIELASEK
KENNETH RICKER

Department of Neurology,
Julius-Maximilians-Universität, Würzburg, Germany

KATRIN ADLKOEFER
UELI SUTER

Institute of Cell Biology, Swiss Federal Institute of
Technology (ETH), Zürich, Switzerland

Correspondence to: Professor Klaus V Toyka, Department of Neurology, Julius-Maximilians-University, Josef-Schneider-Strasse 11, D-97080 Würzburg, Germany. Telephone (+) 931-201-5751; fax (+) 931-201-3546.

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Anaphylactoid reaction to intravenous methylprednisolone in a patient with multiple sclerosis

Exacerbations in multiple sclerosis are treated with short courses of high dose intravenous methylprednisolone. Treatment with intravenous methylprednisolone has mainly minor side effects such as transient flushing, a brief disturbance of taste, insomnia, and mild weight gain.¹ An anaphylactoid reaction after intravenous methylprednisolone treatment has been described in only one patient with multiple sclerosis.² We report on a patient with multiple sclerosis who developed an anaphylactoid reaction on high dose intravenous methylprednisolone treatment. Additional investigations were performed to elucidate the mechanism of this reaction to intravenous methylprednisolone.

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 faeces. On admission 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, paraplegia, 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 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 also 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. Clemastine 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 1000 mg dose 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 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 reactions. Our patient developed 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 appeared with a mean 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.³ 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 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.⁴

Reviewing the literature we found only one case report of a patient with multiple sclerosis who developed an anaphylactoid reaction to intravenous methylprednisolone.² 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.

Allergic reactions to oral or intravenously administered corticosteroids in patients have been found but occur infrequently (0.3% of the patients).⁵ Risk factors for developing allergic reactions after receiving intravenous methylprednisolone are asthma and aspirin intolerance.⁶ Our patient had no history of asthma or other allergic diseases.

Skin tests have been used to investigate the nature of side effects to intravenous methylprednisolone.⁶ 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 an IgE mediated allergy, but could have been caused by fast administration of methylprednisolone leading to high plasma concentrations. However, raised concentrations were not found.⁴ The histamine release reaction for methylprednisolone sodium succinate was not indicative of an IgE mediated reaction. The clinical reaction is possibly 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.

J S P VAN DEN BERG
O R VAN EIKEMA HOMMES
Department of Neurology, University Hospital
Nijmegen, Nijmegen, The Netherlands

E W WUIS
Department of Clinical Pharmacy, University Hospital
Nijmegen, The Netherlands

S STAPEL
Department of Allergy, CLB, Amsterdam,
The Netherlands

P G M VAN DER VALK
Department of Dermatology, University Hospital
Nijmegen, The Netherlands

O R van Eikema Hommes
Multiple Sclerosis Centre Nijmegen, Nijmegen,
The Netherlands

Correspondence to: Dr JSP van den Berg, Department of Neurology, University Hospital Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Telephone +31-24-3618860; fax: +31-24-3541122; email: J.vandenberg@czoneu.azn.nl.

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CORRESPONDENCE

Unilateral auditory hallucinations: ear or brain?

Brasić and Perry¹ convincingly describe a boy with unilateral otopathic auditory hallucinations. However, their literature review is very misleading, postulating dubious 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 Toulouse (1892), who reviewed 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 aggravated by alcohol, sounds of a bell and water in his right, impaired hearing in his left ear (thought 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.² 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 noted six cases from Hecaen and Ropert 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 rotatory vertigo but no otological investigations; three of Penfield's cases with brain tumours 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 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 (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 this, procaine causes 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 1968 review of sensory deprivation by Petrella *et al* was cited as an example of auditory hallucinations from sensory disinhibition. I reviewed some of this literature,⁴ 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 misnomer; in many experimental situations 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 ("silence has a permanent noise running through it"), yet had never complained of tinnitus. Sensory deprivation is more likely than deprivation, as in fact misprinted!

A similar case to that of Brasić and Perry¹ throws considerable light on pathophysiological processes involved. Both were tormented by voices of devils while having symptoms of unilateral ear disease; saw devils and animals interchanging; had fiery visions (fire surrounded by cockroaches, devil transforming into burning wisp of straw); possible fluid in one middle ear (blocked grommet plus air-bone gap; filthy discharge from one ear). Conspicuously omitted¹ was any mention of tinnitus, the most likely generator of the

auditory hallucinations. Fortunately, the other case was Martin Luther,⁵ who clearly described ringing in his ears, unendurable buzzing, thundering, cracks, thumps, etc. Once, he had a musical hallucination (bells of specific churches) while awake 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 otosyphilis, and there was good evidence that he had "French disease".

If Brasić 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 failed⁵ (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.

A G GORDON

32 Love Walk, London SE5 8AD, UK

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Brasić and Perry reply:

Gordon conjectures that otological pathology is the necessary and sufficient condition for auditory hallucinations. We disagree. We hypothesise that auditory hallucinations have many aetiologies which can be 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.¹ For example, in response to minimal environmental stimuli, diseased cochlear hair cells may generate random frequencies producing white noise perceived as tinnitus in some persons. Auditory hallucinations may also result from neurological illnesses,² including after right temporal lobectomy for intracerebral hemorrhage without seizures.¹ We are preparing a manuscript concerning 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 reduced responses of the temporal cortex to external auditory stimuli. Therefore, auditory hallucinations in some patients with schizophrenia may correspond with maximal activation of the auditory association cortex.⁴ The physiology of thinking in words was assessed utilising PET in six persons with schizophrenia who experienced auditory hallucinations, six persons with schizophrenia