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This is the first demonstration of neurotoxicity 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 neuropathy.

US was supported by a grant from the Swiss National Science Foundation and KVT and JZ by University funds.

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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. An anaphylactoid reaction after intravenous methylprednisolone treatment has been described in only one patient with multiple sclerosis. We report 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 paresthesia 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 hands and upper 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 immunological production of IgG and IgM. Brain MRI and the cerebral 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 hydrolyzes 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 an asthma 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 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 reaction. 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 were not found. Clastometry was performed to give the patient. A large amount of methylprednisolone (more than 250 µg/test) resulted in basophil histamine release. However, this positive result was also found when leucoocytes 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 collected 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 µg/ml, 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.

Methylprednisolone 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 reactivity, 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. It could have been caused by 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?

Brasí and Perry convincingly describe a boy with unilateral otopathic auditory hallucinations. However, their literature review is very much biased towards their own 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 to the study 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 agitated by thalamic disease; the 1892 case, abolished by thalamic removal. Far from implicating the brain, this review of musical hallucinations strongly implicates the ear. Even if thalamic 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 (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 Ketter et al procaine causes cochlear hyperacoustisation (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 Petrela 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 non-specific phenomenon; musical hallucinations when 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 dyslectic patient who had never known silence ("there has been a permanent noise running through it"); he had no tinnitus. Their conclusion was that musical hallucinations result from increased activity in the thalamus. Sensory deprivation is more likely than deprivation, as in fact misprinted!

A similar case to that of Brasí and Perry throws considerable light on pathophysiological processes involved. Both were tormented by voices of demons; Brasí suffering symptoms of unilateral ear disease; saw himself as heard by those hearing him; had periodic after-sensations; had auditory hallucinations: the voice was heard by others; Brasí had a continuous hissing noise in his right ear, considerably louder than deprivation, 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.

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