LETTERS TO THE EDITOR

Exacerbation of epilepsy by obstructive sleep apnoea

Identification and avoidance of factors that trigger or exacerbate seizures is important in patients with epilepsy. The most common factors are sleep disturbance, alcohol ingestion, drugs, stress, and photosensitivity. The present case is the first report of seizures exacerbated by obstructive sleep apnoea. Treatment with continuous positive airway pressure (CPAP) given through a nasal mask abolished nocturnal seizures and greatly reduced the frequency of daytime attacks.

The patient, now aged 30 years, was born three weeks prematurely. Moderate mental retardation was noted at the age of five years and subsequent chromosomal analysis disclosed a balanced translocation t(3:22) with the 3p terminal deleted and the non-reciprocal translocation t(14:11) with the 11q terminal deleted. Dysmorphic features associated with trisomy 18 include growth retardation and congenital heart defects, cerebral anomalies, and congenital anomalies of the limbs, eyes, ears, and nasal bones, hypertelorism, and a short palate.

Because of a history of loud nocturnal snoring and daytime hypersomnolence, the patient underwent a sleep study. Overnight snoring and daytime hypersomnolence, the patient underwent a sleep study. Overnight polysomnography showed an average of 30 episodes of desaturation to below 90%, each episode lasting 20 seconds. The cyclical dips were associated with upper airway obstruction, consistent with the syndrome of obstructive sleep apnoea. At the time of the examination, the patient was taking the antiepileptic medication carbamazepine (400 mg twice daily), gabapentin (150 mg twice daily), and clonazepam (10 mg at night). The diagnosis was obstructive sleep apnoea syndrome and snoring.

The patient tolerated the CPAP mask well and his snoring was abolished. A repeat sleep study showed that nocturnal oxygen saturation averaged 97% with no significant dips. An immediate improvement in daytime alertness was noted. On follow up three months later, all the nocturnal attacks had been abolished and his daytime tonic seizures were reduced to two per week, without falling. His daytime alertness remained much improved and he no longer had morning headaches. The improvement has now been maintained for more than two years.

Obstructive sleep apnoea typically presents with daytime sleepiness and restless and un-refreshing and restless nocturnal sleep.1 It is usually associated with obesity but may also occur in patients with nasopharyngeal abnormalities and in patients taking sedatives or alcohol. The diagnosis depends on awareness of the condition and can be confirmed by sleep studies. Treatment with nasal CPAP is often successful but surgery to correct significant narrowing of the nose or pharynx is sometimes required.1 In the present patient, the obstruction was related to his dysmorphism, but the sedative effect of his antiepileptic medication may also have contributed.

Obstructive sleep apnoea may have exacerbated this patient’s epilepsy simply by producing interrupted and un-refreshing sleep. Sleep deprivation is a potent trigger for seizures.2 Alternatively, the hyposaemia associated with the obstructive sleep apnoea may have triggered the seizures. Hyposaemia is known to precipitate seizures in patients with epilepsy.3

Obstructive sleep apnoea should be considered as a cause of poor seizure control in any patient with disturbed sleep, as the correct diagnosis can lead to highly effective non-pharmacological treatment. Failure to make the correct diagnosis can result in the patient being treated with more antiepileptic medication that could exacerbate obstructive sleep apnoea and thereby worsen seizure control.

Since submitting this communication, Tirosh and colleagues reported four boys with neurodevelopmental deficits and obstructive sleep apnoea. Treatment with CPAP produced several clinical benefits including a significant decrease in seizure frequency in one boy.

We thank Dr CI Roberts who referred the patient.

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Fibrolipomatous hamartomas of the proximal ulnar nerve associated with macrodactyly and macrodystrophy: a case report

Fibrolipomatous nerve tumours are rare benign tumours that are usually slowly progressive and that predominate in the median nerve at the level of the wrist and hand, usually causing carpal tunnel syndrome.1 The tumour is sometimes associated with macrodactyly and lipomatous macrodystrophy of muscles and subcutaneous fat in the region supplied by the affected nerve.2,3

In this report we focus attention on fibrolipomatous hamartoma at a previously undescribed location: an unusual cause of carpal tunnel syndrome. Furthermore, we point out that on the basis of the characteristic features of fibrolipomatous hamartoma on MRI, a non-invasive diagnosis can be made.

The 15 year old male patient was born with a giant fourth finger (about twice as thick as the neighbouring fingers) of the right hand which grew proportionally with the other fingers during early childhood. The family history was unremarkable. For cosmetic reasons, the finger was amputated at the age of three. When the patient was 27 years old, she experienced hypoaesthesia and paraesthesia in the cutaneous area of the right ulnar nerve and a stubbing pain in the ulnar arm. She also noticed a slight weakness in the flexion of the fourth and fifth fingers, of wrist flexion, and flexion of the hand muscles innervated by the ulnar nerve. At the same time, she noticed a thickening of the elbow at and above the elbow, with electrical sensations elicited by nerve percussion. During the next eight years, the symptoms progressed. Recently, a clinical examination disclosed the sensory deficits mentioned above and weakness of muscles supplied by the ulnar nerve (MRC grade 3). The ulnar side of the forearm and the hypothenar and the little finger showed hypesthesia. Hypertrophy of the elbow was restricted by a palpable sausage-like elastic tumour in the sulcus nervi ulnaris and the distal upper arm. There were no naevi, angioma, or neurofibroma.

In nerve conduction studies the maximal motor conduction velocity over the elbow nerve segment was 44 m/s on the affected and 57 m/s on the non-affected side and the amplitudes of the elicited muscle potentials in the abductor digiti minimi muscle were reduced to 0.6 mV. Antidromic sensory nerve action potentials could not be elicited in the right ulnar nerve with stimulation at the wrist or proximal to the elbow. Electromyography disclosed signs of chronic neurogenic changes in all muscles supplied by the right ulnar nerve. Clinically and electromyographically the diagnosis of carpal tunnel syndrome was made.

T1 weighted MRI of the right upper arm and elbow (figure A-D) showed a fusiform enlargement of the ulnar nerve, with an extension from 6.5 cm proximal to 2 cm distal to the olecranon. The ulnar nerve diameter of the nerve tumour was 2.3 cm. The coronal section showed serpentiniform fibrous components within the nerve (figure A). On the axial section through the upper arm 6 cm proximal to the olecranon, circular structures of fatty and fibrous tissue could be seen within the nerve (figure B). The nerve had its largest diameter within the sulcus nervi ulnaris and mainly consisted of fibrous tissue. Figure C shows a bulb-like configuration on the
axial slice (figure C). At the entrance to the cubital tunnel, the nerve was compressed by the transverse fibres of the arcuate ligament (figure A and D). Here, the nerve seemed pathologically hypointense, indicating a fibrous degeneration of the nerve induced by compression. In T1 weighted MRI of the forearm, the ulnar nerve was surrounded by fatty tissue and had a normal diameter in its course along the forearm. The flexor digitorum profundus and flexor carpi ulnaris were found to be increased in volume and had a high content of intramuscular fat (figure E). In the distal forearm, fatty tissue infiltrated the spaces between the tendons and the muscle bellies. The blood vessels were of normal diameter.

The patient has a non-hereditary congenital malformation, with a combination of a slowly progressive fibrolipomatous hamartomatous tumour of the ulnar nerve at an unusual location in the elbow region, unusual macrodactyly of a single finger, and lipomatous dystrophy of soft tissues remains obscure. Besides others, a neurogenic cause has been discussed on the basis of findings in neurofibromatosis.

Fibrolipomatous hamartoma is usually located in the distal median nerve and causes carpal tunnel syndrome. Only one case of fibrolipomatous hamartoma proximal to the elbow, in the brachial plexus, has been described before. In our patient, MRI detected an enlarged flexor carpi ulnaris muscle and a thick ulnar nerve as a previously unmentioned combined cause of a clinically relevant ulnar nerve entrapment in the proximal and distal part of the cubital tunnel. The proximal fibro-osseous tunnel is formed by the medial collateral ligament and the distal sulcus nervi ulnaris; the distal part of the tunnel is formed by the humeral and ulnar insertions of the flexor carpi ulnaris muscle and the arcuate ligament. Furthermore, the massively thickened nerve can also be mechanically lesioned within the sulcus nervi ulnaris by flexion-extension movements in the elbow.

The differential diagnosis of a palpable, unilocular fusiform nerve enlargement comprises fibrolipomatous hamartoma, lipomas within the nerve sheath, and segmental or plexiform neurofibromatosis. In our patient,
MRI disclosed serpiginous nerve fascicles surrounded and separated by fibrous and fatty tissue within the expanded nerve sheath as typical features of fibrolipomatous hamartoma. Fibrolipomatous hamartoma can clearly be distinguished from lipomas within the nerve sheath, which are characterised by foci that dislocate and compress the normal nerve bundles, and from segmental and plexiform neurofibromatosis, in which the nerve fibroma has MRI signal characteristics of soft tissue and not of fat. Furthermore, in plexiform neurofibromatosis, the tortuous nerve is studded by small tumours.

The unique features of fibrolipomatous hamartoma as identified by MRI allowed the identification of this benign nerve tumour preoperatively. This facilitates the decision to decompress affected nerves at the preferential sites of nerve entrapment and helps to avoid diagnostic nerve biopsy or even resection of an ambiguous nerve tumour.

A long TR/long TE (2000/80) MRI showing a fairly well defined area of hyperintensity on the right occipital lobe.

had an excellent outcome, except for recurrent generalised seizures due to a residual lesion in the right occipital lobe, shown by CT. The patient was treated with oral 100 mg phenytoin thrice daily and required haemodialysis due to the progressive worsening of his renal function owing to chronic organ rejection. One year later, he was admitted to our hospital because of fever of unknown origin. A few days after admission, he developed a focal epilepticus characterised by stupor, tonic deviation of the eyes to the left, full dilatation of the right pupil with sluggish reaction to light, clonic movements of the left face, and left hemihypesthesia with hypeflexia and extensor plantar response. No previous clinical movements were seen on plegic limbs. Meanwhile, left pupil responses remained normal. Laboratory studies showed evidence of chronic renal failure and the serum concentrations of phenytoin were 5 µg/ml (reference range 8-20 µg/ml). After intravenous administration of 1000 mg diphenylhydantoin, the seizures stopped and simultaneously the pupillary dilatation disappeared. Thereafter, pupillary assessment showed no abnormalities. The left hemiparesis and extensor plantar response were transient postictal findings. A long TR/long TE (2000/80) MRI showed a fairly well defined area of hyperintensity on the right occipital lobe, without any sign of a mass effect. Lumbar puncture disclosed a clear CSF under normal opening pressure, with no pleocytosis and containing normal amounts of glucose and proteins; microbiological studies were negative. Several hours after the status had finished, an EEG disclosed sharp spikes and slow waves over the right temporo-occipital region. The patient responded to empirical antibiotic therapy. The clinical course was uncomplicated and the patient continued on phenytoin, being free from seizures after one year of follow up.

Our patient showed a focal status epilepticus with right pupillary dilatation and tonic deviation of the eyes and head to the left; other associated clinical features were clonic movements of the left face and left hemiplegia. All these phenomena disappeared dramatically on phenytoin treatment, thus indicating their epileptic pathogenesis. Although an ictal EEG was not recorded, major although indirect arguments in favour of a right occipitotemporal onset are the interictal EEG spikes as well as the MRI lesion located on that area.

Hemiplegia may be a well known negative ictal phenomenon. Its association with clinical movements at other levels, as seen in our patient, suggests its ictal mechanism. The absence of previous convulsions on plegic areas further supports that idea. The concomitance of clonic and tonic seizures has only been previously described in a few series and is a very uncommon clinical pattern. However, it is difficult to ascertain that such paresis in this case is directly due to neuronal discharges. Postictal (Todd’s) paralysis may appear in the context of partial status epilepticus probably due to intravascular fluid changes; this could be another explanation for the hemiplegia in our patient.

Unilateral mydriasis during fits should arouse the suspicion of brain herniation and provide evidence of a contralateral hemispheric lesion. Five patients showed the pupil abnormality contralateral to the epileptic scalp EEG focus and three had ipsilateral mydriasis.

The exact pathophysiology of pupil changes during seizures remains unclear; it has been stated that miosis could represent an excitatory component whereas dilatation would be interpreted as a negative ictal phenomenon. Descending inhibition of the Edinger-Westphal nucleus would result in pupillary dilatation and impaired pupillary light reflex; this could be mediated by leu-enkephalin fibres which may produce pronunced inhibition of this nucleus in experimental studies. Animal experiments performed in macaques showed that electrical stimulation of the anterior occipital lobe produced contralateral ocular deviation with asymmetric dilatation of both pupils that was greater in the homolateral eye; these features were found in our patient, although we did not see changes in the diameter of the left pupil and the reason for this disparity is unknown. This finding was by contrast with the contralateral mydriasis obtained when the frontal eye field was stimulated and in patients with frontal epilepsy. The exact anatomical basis for the changes in pupil diameter during fits remains to be elucidated although the reports and experiments commented on herein, including our case, indicate that an ictal pupil dilatation found in a patient with contralateral epileptic movements suggest occipitotemporal pathology on the same side as the mydriasis; if all these changes are ipsilateral, a frontal lesion should be suspected on the opposite side.


Ipsilateral mydriasis in focal occultotemporal seizures

Occipital epilepsy is characterised by seizures which usually begin with oculomotor or elementary visual symptoms and often spread to other cortical and subcortical regions. We think that the present case report is of particular interest because of the nature of partial status comprising positive (clonic jerks of eyes and left face) and negative motor components (left hemihypesthesia) with dilatation of the right pupil. These clinical features were shown to be related to a lesion in the right occipital lobe by MRI and EEG. To our knowledge, the association of these data has not been previously reported.

A 37 year old man had a history of chronic renal failure due to an idiopathic mesangio-proliferative glomerulonephritis since he was 20 years old. He underwent a renal transplantation which was unsuccessful because of an arteriothrombosis. Two years later, a second kidney was transplanted to the patient. Shortly afterwards, while he was immunosuppressed with steroids and azathioprine, he had a Listeria monocytogenes meningocencephalitis. Treated promptly with ampicilline, he...
In 1988 Straube and Sigel reported on a 56 year old patient with a bilateral Parkinson's syndrome, including resting tremor, rigidity, bradykinesia, and a favourable response to levodopa medication, starting at the age of 51 years. This patient was discovered to have a tumour (anaplastic astrocytoma, grade WHO III). She was retreated with a cause trial of x rays and cortisone. Under this treatment, her parkinsonian syndrome (shuffling gait, resting tremor, on-off fluctuations, freezing episodes) deteriorated transiently for about 10 weeks. This deterioration seemed to distinctly exceed potential x-ray/cortisone induced side effects, as for instance manifested by fatigue and equilibrium disturbances. After cessation of the treatment, the parkinsonism gradually improved to the previous stage over a period of six months in combination with increased levodopa/dopamine agonist dosages.

In conclusion, the proposal of the previous report that a tumour in the supplementary motor area may cause a parkinsonian syndrome is withdrawn. At present we are not interested in this investigation.

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### Spect-IPT values

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<th>March 1995</th>
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<td></td>
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<tr>
<td>Striatum right</td>
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<tr>
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<tr>
<td>Putamen left</td>
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<tr>
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<tr>
<td>Mean (SD)</td>
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<td>2.2</td>
<td>6.5 (1.4)</td>
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SPECT was performed 90 to 120 minutes after injection of 150 MBq IPT. After reconstruction by filtered backprojection transverse slices corrected for attenuation were realigned parallel to the AC-PC line. For semiquantitive evaluation of specific [I-123]IPT binding ratios between striatum, caudate, putamen, and background regions were calculated. Specific uptake ratios were defined as mean counts per pixel in the respective region of interest minus mean counts in a background region divided by the mean counts in the background region. The uptake ratios obtained in the patient studies and in age matched controls are listed in the table. The increased IPT binding in the left putamen in the 1996 study is most probably due to an artefact caused by a spot of high background activity accidentally located around the putamenal region of interest in this investigation.
aware of a case reporting a levodopa responsive parkinsonian syndrome with a tumour in the supplementary motor area. Certainly, the criteria “responsiveness to dopaminergic drugs” may help to differentiate tumour induced parkinsonism from the concomitant idiopathic disease. Interestingly, Dick and coworkers reported on a patient with an infant in the supplementary motor area, who had bradykinesia, but not from rigidity, which might suggest that the symptoms “rigidity” may be suitable to differentiate tumour-induced versus concomitant parkinsonian syndrome. Furthermore, in rare cases, in which patients with parkinsonism with CNS tumours respond favourably to dopaminergic medication (to our knowledge only one case report1), modern imaging techniques with specific ligands to presynaptic terminals of the strionigral pathway further aid in differentiating between a tumour induced syndrome and comorbidity.

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**Hereditary neuromyotonia: a mouse model associated with deficiency or increased gene dosage of the PMP22 gene**

Neuromyotonia is characterised by increased muscle stiffness caused by hyperactivity of motor units. Clinical characteristics are increased stiffness and cramping on intended muscle contraction, slowed relaxation, and myokymia. Neuromyotonia is a heterogeneous condition. In the acquired form, autonomicity against peripheral nerves seems to play a pathogenic part. Neuromyotonia may occasionally follow immune mediated polynuropathy. Antibodies against voltage gated potassium channels have been detected in some cases. In the hereditary forms, neuromyotonia may occur in isolation or in association with hereditary neuropathies. We here report on neuromyotonia developing in aged mice homozgyous deficient for or carrying an increased gene dosage of PMP22. Null mutants display a severe dysmyelinating neuropathy characterised by tomaculum formation and subsequent myelin degeneration resembling human hereditary neuropathy with pressure palsies (HNPP). Nerve conduction studies show a profound slowing of compound nerve action potentials (CMAPs). Despite these profound peripheral nerve abnormalities, mice did not show overactivity up to 12 months. Between the ages of 12 and 14 months, we found progressive overactivity with tonic stretching of the hind limbs and increased cramping of the small foot muscles augmented on voluntary contraction, and generalised myokymia including the whisker muscles in all three PMP22 deficient mice examined. These signs persisted during general anaesthesia. On needle EMG, we found serial high frequency bursts of motor units in the gastrocnemius, quadriceps, and small foot muscles (figure, A). Some of the discharges were doublets, triplets, or multi-plets (figure, A and B). In addition, we found continuous myokymic muscle fibre activity (figure, B). Sciatic nerve transmission at the sciatic notch did not abolish the overactivity indicating a peripheral nerve generator. In five 14–18 month old mice heterozygously deficient for the expression of PMP22 and with the typical electro-physiological signs of a dysmyelinating neuropathy, we found neuromyotonia only in one out of three animals at a single site in the gastrocnemius muscle. We also found severe neuromyotonia in a transgenic mouse model with an increased PMP22 gene dosage at one year of age (data not shown). These overexpressing mice have a severe hypomyelinating neuropathy in which Schwann cell development is arrested in a hyperproliferative and premyelination-like state. This suggests that the occurrence of neuromyotonia is linked to the PMP22 gene dosage. We did not find abnormal nerve conduction, repetitive CMAP or neuromyotonia in four 13 month old control mice with normal PMP22 expression.

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**EMG recordings from a 14 month old mouse deficient for the expression of the peripheral myelin protein PMP22.**

The mouse was anaesthetised with Hypnorm (Janssen, Beersel, Belgium) and investigated using a Tennes electromyograph with a concentric needle electrode. (Medelec DFC25, 0.3 mm diameter, recording area 0.019 mm²). (A) Multiple discharges in the small foot muscles. (B) Representative recording of myokymic discharges and doublets from another mouse (PMP22−/−). There was abundant myokymic motor activity, but no voluntary limb movements during these recordings.
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 even- tually help to define the pathogenesis and mode of treatment of hereditary forms of human neuro-myotonia.

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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, 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 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 muscle cramps in her arms and 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 moderate 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 cerebrospinal fluid revealed multiple white matter lesions. Additional investigations excluded other diseases—for example, borborellis 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 an additional 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-gioedema. 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 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 reaction. 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 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 Osher. 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 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.

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.

Allergic 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 allergic diseases.

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 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. The histamine release reaction for methylprednisolone sodium succinate was not indicative of an IgE mediated reaction. The clinical reaction appeared to a (dose related) toxic effect of methylprednisolone on the basophil granulocytes. In conclusion, the clinical symptoms which developed during high dose intravenous methylprednisolone treatment could not be caused by basophil granulocytes. 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.

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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 music 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 cases reported without structural brain lesions, two with pronounced deafness, the third with attacks of nausea and rotary vertigo but no otological investigations; three of Penfield’s cases with brain tumours but no ear or hearing examination. So the last three 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 view of the link between epilepsy and the ear, it is noteworthy that the EEG changed from an awake pattern to seizure activity.

The1992 study on and deprivation by Petrella et al was cited as an example of auditory hallucinations from sensory disinhibition. I reviewed some of this literature, concluding that for results to be valid 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 Brasic and Perry’ 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 (“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!

Their physiology of thinking in words was assessed utilising PET in six patients with schizophrenia who experienced auditory hallucinations, six persons with schizophrenia with auditory hallucinations. Fortunately, the other case was Martin Luther, who clearly described ringing in his ears, unendurable buzzing, thuddering, thumps, thumps. 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 Brasic 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 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 medical 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


Brasic and Perry reply: Gordon conjectures that otological pathology is the necessary and sufficient condition for auditory hallucinations. We disagree. We hypothesize that auditory hallucinations have many aetiological which can be classified as otological, neurological, neuropsychiatric, and combined. Auditory hallucinations may result from the multiple effects of otology, such as altered signal transduction in hair cells. 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, including after right temporal lobectomy for intracerebral hemorrhage without seizures.

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. The physiology of thinking in words was assessed utilising PET in six persons with schizophrenia who experienced auditory hallucinations.
who did not experience auditory hallucinations, and six normal controls. Imaging sentences spoken by another person activated the left middle temporal gyrus and rostral supplementary motor area of normal controls and schizophrenic patients without auditory hallucinations, but not schizophrenic patients with auditory hallucinations. Thus, some people with schizophrenia with auditory hallucinations seem to lack activation of portions of the brain associated with the monitoring of inner speech. These reports suggest that auditory hallucinations in schizophrenia are correlated with physiological abnormalities of regional cerebral blood flow in the left auditory association cortex and rostral supplementary motor area. Auditory hallucinations also are associated with combinations of otological, neurological, and neuropsychiatric disorders. For example, our patient had conductive hearing loss, bilateral tinnitus, and psychosis. We agree with Gordon that a thorough otological history and examination including audiology is a necessary component of the assessment of a person with auditory hallucinations.

JAMES ROBERT BRASIC
Richard Perry
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Correspondence to: Dr. Brasic, Department of Psychiatry, New York University School of Medicine, 550 First Avenue, New York, New York 10016-6497 USA. Telephone (212) 562-4764; fax (212) 263-8135.


Cu/Zn superoxide dismutase gene mutations in amyotrophic lateral sclerosis: correlation between genotype and clinical features

We refer to the article by Radunovic et al and the kindred referred to in this article and in the article by Cleveland et al as the Australian superoxide dismutase (SOD1) Gly37Arg familial amyotrophic lateral sclerosis (FALS) kindred. From an extraordinary kindred mutations in the same gene are responsible for a variety of misfolded proteins in two separate continents. Investigations in Australia, subsequent to the publication of the paper by Cleveland et al, identified the mutation in this family as His43Arg, not Gly37Arg. The mutation was identified as H43R by heterozygote sequencing and sequencing of the single strand conformation polymorphism (SSCP) seen in exon 2 from several affected family members from the kindred. The original designation of the kindred as Gly37Arg must have arisen from a sample mix up between Western Australia, North Carolina, and Chicago. It is a relief to those of us living in Australia that this country may not after all pose an extra hazard to those carrying this SOD1 mutation. The clarification of the mutation in the family adds further weight to the data showing that different mutations may to some extent correlate with different rates of progression of FALS. The kindred has been reported correctly as His43Arg by Juneja et al. It is particularly large kindred with over 500 known family members, there are 20 cases of FALS known to have this SOD1 gene mutation. Risk of having inherited the family mutation. The family is so large that on its own it represents a significant problem for genetic counselling in Western Australia. Twenty family members have received presymptomatic genetic counselling. The mutation in the kindred has been reported in a Huntington’s-like protocol based on the results of an exome 2 mutation.


C. Radunovic and Leigh reply: We are grateful to Drs Laing and Siddique for pointing out the error in the designation of the Australian His43Arg kindred as Gly37Arg. A Gly37Arg kindred with different phenotype to the Australian kindred, however, exists in Turkey. We are therefore still concerned that it is too early to predict particular ALS phenotypes based on the site of a CuZnSOD1 gene mutation. We are also worried about the lack of clinical information provided in reports on the CuZnSOD1 gene mutations, and a lack of evidence as to where these kindreds come from. For example, it is very likely that the Gly37Arg kindred reported by Juneja et al is the same one as reported by Cudkowicz et al. All these create confusion and we would like to see a centralised pedigree database established where detailed but anonymous phenotype and genotype data can be deposited and accessed. It is only by collating all of the available information that comments on prognosis can be made.

C. Radunovic
Department of Clinical Neurosciences, Institute of Psychiatry and King’s College School of Medicine and Dentistry, London, UK

BOOK REVIEWS


The modern day neurologist attempting to maintain a semblance of current knowledge on multiple sclerosis has an awesome task ahead of him. A brief perusal of Medline will give him some idea of the size of this problem. The kindred has been reported in a Huntington’s-like protocol based on the results of an exome 2 mutation.


seems to be a little impenetrable, the section on the epidemiology of epidemics seems to hardly have changed in 20 years despite alternative published analysis and the slant on disease modifying treatments is unsurprisingly North American. However, overall this is a book which I would recommend any interested physician to have on their shelves and it can do little else but enhance their clinical practice.

NEIL ROBERTSON


Although from its title this is a book for the neurosurgeon and orthopaedic surgeon, it will, I am sure, prove invaluable for the medical neurologist and indeed for all those who may be concerned with the effects of trauma on the central and peripheral nervous system.

In so far as each aspect of neurological damage has its own author and chapter (and there are 42 chapters), I feared that there might be considerable overlap but fortunately, this is not so. Whether this happy state of affairs results from firm action on the part of the editors or great sense on the part of the authors is not clear but I am sure that there was some editorial control.

In preparing opinions which may be needed in Court it is always well to be able to back one's opinions with appropriate literature and in this respect the book should prove invaluable. There are references at the end of each chapter which amount to 27 pages of references in the book as a whole.

DAVID SUMNER


The incidence of epilepsy rises sharply over the age of 60 and with an ever-increasing elderly population, it is becoming an area of increasing clinical and social importance. The limitations of current knowledge, especially in relation to treatment and directions for future clinical research, are considered in a valuable penultimate chapter of this book, that would have been well placed at the beginning.

The book is divided into five sections: epidemiology; pathophysiology of aging and relation to seizures; diagnosis; medical treatment; and future directions. The epidemiology is becoming increasingly understood and is well summarised. There is a very good chapter on pathological processes in elderly people causing seizures and an excellent theoretical and practical guide to falls in elderly persons. In many chapters the book tends to stray a little from its title and considers more general problems of epilepsy with relatively little that is specific to elderly people. This probably reflects the paucity of published information. It is, however, taken to extremes in detailed chapters on alteration of renal and glucose homeostasis in elderly persons, which really only contain passing references to epilepsy. Chapters on the differentiation of pathological changes of EEG and MRI in elderly people from age related variants are highlights in the diagnosis section. There are two chapters devoted to status epilepticus in elderly people. They contain valuable information but conflict in various aspects partly because they use different classifications. The treatment section has a strong emphasis on pharmacokinetics. Treatment is considered on a drug by drug basis, including established and newer drugs, essentially from an American perspective. More space is given to felbamate (not available in the United Kingdom) than to any other new drug. None of the (admittedly few) comparative trials of drugs in elderly people is mentioned and nowhere are guidelines for treatment suggested.

This book is easy to read and has some very useful chapters, but is patchy, which is perhaps inevitable, given the current state of knowledge.

MARK MANFORD
VOLUMES 62 and 63. ASSESSORS

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