NGF concentrations in human cerebral arteries

Artery	*Number*	*NGF (ng/g) Mean (SEM)*
Anterior cerebral (AC)	7	0·82 (0·19)
Internal carotid (IC)	7	0·78 (0·16)
Posterior cerebral (PC)	7	2·02 (0·53)
Superior cerebellar (SC)	7	2·14 (0·45)
Posterior communicating	6	1·87 (0·58)

P values were determined by student's *t* test.
AC *v* SC $P < 0.02$; IC *v* PC $P < 0.04$; IC *v* SC $P < 0.015$.
Mean NGF concentration *v* age of subject $r = -0.8$, $P < 0.034$.

ache, as in temporal arteritis, and also reduce NGF synthesis, which is increased by inflammation.[1] Modulation of NGF activity may thus provide a new approach to prevent and treat vascular headaches.

We thank Dr D Sinicropi and Dr R Williams-Chestnut of Genentech, Inc, USA for the NGF antibody.

P ANAND
A PARRETT
Department of Neurology, St Bartholomew's and Royal London School of Medicine and Dentistry, Whitechapel, London E1 1BB, UK
L CHADWICK
P HAMLYN
Department of Neurosurgery, St Bartholomew's and Royal London Hospitals, London, UK

Correspondence to: Dr P Anand.

1 Anand P. Neurotrophins and peripheral neuropathy. *Philos Trans R Soc Series B* 1996; **351**:449–54.
2 Anand P, Parrett A, Martin J, *et al.* Regional changes of ciliary neurotrophic factor and nerve growth factor immunoreactivity in spinal cord and cerebral cortex in human motoneurone disease. *Nature Medicine* 1995;**1**:168–72.
3 Edvinsson L, Ekman R, Jansen I, *et al.* Peptide-containing nerve fibres in human cerebral arteries: immunocytochemistry, radioimmunoassay and in vitro pharmacology. *Ann Neurol* 1987;**21**:431–7.
4 Gavazzi I, Cowen T. NGF can induce a 'young' pattern of re-innervation in transplanted cerebral blood vessels from ageing rats. *J Comp Neurol* 1993;**334**:489–96.
5 Moskowitz MA. The neurobiology of vascular head pain. *Ann Neurol* 1984;**16**:157–68.

Triphasic waves in serotonin syndrome

The serotonin syndrome was first described in 1960 in depressed patients with delirium due to monoamine oxidase inhibitors and L-tryptophan administration.[1] Symptoms of the serotonin syndrome include mental status changes, behavioural changes, myoclonus, rigidity, hyperreflexia, and autonomic instability with low grade fevers, diarrhoea, headache, tachycardia, and pupillary dilatation.[2] The serotonin syndrome has been noted to occur with several serotomimetic agents, particularly when multiple agents are used.[3]

Psychiatry and pharmacology literature has described the serotonin syndrome for several years. As the use of serotonin reuptake inhibitors has increased, cases have begun to appear in the neurology literature—often associated with combination regimens that include serotonin reuptake inhibitors and dopaminergic agents. These cases have been attributed to the serotomimetic effects of dopamine and its agonists. I describe a patient admitted for acute confusion who met criteria for the serotonin syndrome, responded well to supportive care, and whose EEG showed prominent triphasic wave activity.

A 76 year old man had a history of Parkinson's disease, recurrent depression, chronic constipation, and non-insulin dependent diabetes mellitus. He had right sided tremors, bradykinesia, hypophonia, and significant gait instability with occasional visual hallucinations. Due to his depression and concerns regarding the use of tricyclic antidepressants in a patient already at risk for autonomic dysfunction, he was started on 50 mg sertraline at bedtime. He initially responded well, experiencing no notable side effects. About three days before admission, amantidine was added to his drug regimen which already included sertraline and Sinemet. The patient was brought to the emergency department by his wife due to increasing confusion, diarrhoea, and frequent falls that had begun a day earlier.

On examination, the patient had a low grade fever, extreme rigidity in all limbs, agitation, confusion, and ongoing visual hallucinations. Over the next four hours he developed multifocal and startle myoclonus. He had not received any neuroleptic or antibiotic drugs in more than six months.

Electrolytes, creatine kinase, liver functions, a complete blood count, and ammonia concentration were all normal. Blood cultures and urinalysis were also unremarkable. A 16 channel EEG was obtained and showed pronounced triphasic wave activity and diffuse slowing. Supportive care with intravenous fluids and acetaminophen were initiated and all outpatient medications were stopped. Within 24 hours the patient's myoclonus began to subside and in 48 hours he had returned to baseline without any sequelae. He continues to do well on Sinemet alone for his Parkinson's disease.

Case reports of the serotonin syndrome have noted EEG abnormalities—delta range activity, slow waves, spike and waves, and polyspike and waves—but triphasic waves have not previously been reported.[4 5] The diagnosis of the serotonin syndrome in the Parkinson's disease population is a difficult one as many of the features of the serotonin syndrome are present in Parkinson's disease alone. A high level of suspicion for the serotonin syndrome in patients with Parkinson's disease taking serotonin reuptake inhibitors is necessary to make the diagnosis. Electroencephalography may play an important part in the diagnosis of the serotonin syndrome, particularly in the setting of other concurrent neurological disease.

G L DIKE
Department of Neurology, Johns Hopkins Hospital, Pathology 509 600 N Wolfe Street, Baltimore MD 21287, USA.

1 Oates JA, Sjoerdsma A. Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor. *Neurology* 1960;**10**:1076–8.
2 Bodner RA, Lynch T, Lewis L, Kahn D. Serotonin syndrome. *Neurology* 1995;**45**: 219–23.
3 Nierenberg DW, Seprebon M. The central nervous system serotonin syndrome. *Clin Pharm Ther* 1993;**53**:84–8.
4 Insel TR, Roy BF, Cohen RM, Murphy DL. Possible development of serotonin syndrome in man. *Am J Psychiatry* 1982;**139**:954–5.
5 Lejoyeux M, Finejre F, Adis J. The serotonin syndrome. *Am J Psychiatry* 1992;**149**: 1410–11.

Pseudoseizures or non-epileptic seizures (NES); 15 synonyms

Medical jargon is often confusing, particularly when the condition described falls within the domain of two medical specialties. This confusion reaches its zenith with those seizure disorders that do not have an epileptic aetiology. There are at least 15 synonyms for a condition that occurs in 10%[1] to 26%[2] of adults investigated for refractory seizures. This causes confusion for patients, doctors, and researchers. The adoption of a common term must be the rational way forward, but which one to choose?

The label pseudoseizures is the most commonly used. Its great weakness is that it is not acceptable to patients as the label implies that the seizures are not real. The reality of the "fit" is seldom an issue. The label pseudoepileptic seizures is both less well known and pejorative. Labels that are offensive to patients are counterproductive and best avoided.

The aetiology of this disorder is currently a matter for speculation. Terms that imply a psychological causation are misleading. Psychogenic seizures, hysterical seizures, psychogenic attacks, and hysterical attacks are all inappropriate for this reason.

A good descriptive label is non-epileptic attacks but this is seldom used. Non-epileptic attack disorder (NEAD) is rarely used and is complicated. Functional seizures, hysteroepilepsy, pseudoepilepsy, hysterical epilepsy, pseudoepileptic attacks, and psychoseizures are the least commonly used terms. These labels should all be abandoned.

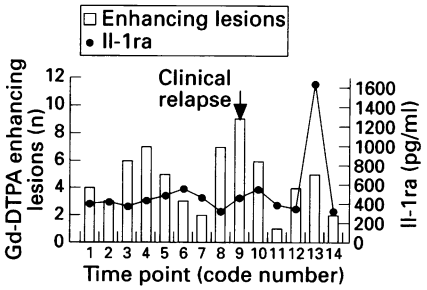
This leaves the term *non-epileptic seizures (NES)* as the favoured candidate; it is non-judgmental, often used, acceptable to patients, and best describes the problem without implying causation.

DAVID A SCULL
Institute of Neurology, Queen Square, London WC1N 3BG, UK.

1 Chayasirisobhon-S, Griggs-L, Westmoreland-S, Kim-CS. The usefulness of one to two hour video EEG monitoring in patients with refractory seizures. *Clin Electroencephalogr* 1993;**24**:78–84.
2 Koblar-SA, Black-AB, Schapel-GJ. Video-audio/EEG monitoring in epilepsy—the Queen Elizabeth Hospital experience. *Clin Exp Neurol* 1992;**29**:70–3.

Multiple sclerosis: longitudinal measurement of interleukin-1 receptor antagonist

Inflammatory activity in multiple sclerosis is regulated by a network of proinflammatory and antiinflammatory cytokines. Identifying downregulatory cytokines opens new potential therapeutic options in multiple sclerosis.[1 2] The interleukin-1 receptor antagonist (Il-1ra) is the only known naturally occurring specific antagonistic cytokine; Il-1ra competes with Il-1 for receptor binding and lacks agonist activity. Il-1ra has been implicated in the pathogenesis of stroke and several inflammatory diseases.[3] Human Il-1ra is available as a recombinant protein; the first controlled study using Il-1ra for therapy (in



Gd-DTPA enhancing cranial MRI lesions (white columns) and serum Il-1ra concentrations (black dots) measured longitudinally during one year in patient 1 with active rr-MS. There was a clinical relapse at time point 9, which was treated with intravenous methylprednisolone. Changes in MRI activity tended to precede changes in serum Il-1ra concentrations by three to four weeks (one time point, $P < 0.05$).

sepsis) was published recently.[4] Its agonist, Il-1β—the predominant Il-1 isoform in humans—is consistently expressed in acute multiple sclerosis plaques.[1] It is conceivable, but so far neither confirmed nor disproved, that the natural specific antagonist Il-1ra is involved in the counterregulation of inflammatory activity in multiple sclerosis. If this were the case, Il-1ra would be a novel candidate for immunomodulatory therapy in multiple sclerosis.

We conducted a pilot study of nine patients with definite multiple sclerosis. The patients were followed up for one year by clinical examination (EDSS) and MRI every three to four weeks (resulting in 14 time points with code numbers 1 to 14), in parallel to measuring Il-1β and Il-1ra concentrations in serum and CSF. Five patients with a relapsing-remitting multiple sclerosis (two men, three women; ages 27–34; duration of disease one to three years), and four patients with chronic progressive multiple sclerosis (one man, three women; ages 40–59; duration of disease five to 28 years) were studied. Cranial MRI (Siemens Magnetom 1·0 Tesla, München, Germany) images were obtained according to standard guidelines. They were T2 and T1 weighted, with and without 0·1 mmol/kg Gd-DTPA enhancement. Serum (n = 118) and CSF samples (n = 33) were frozen within two hours of collection and stored at −80°C. Il-1β and Il-1ra were measured by commercially available enzyme linked immunosorbent assay (ELISA) kits (R and D Systems, Minneapolis, MN; sensitivity 1pg/ml for Il-1β and 20 pg/ml for Il-1ra; intra-assay precision < 8·5%). The assays were performed in a blinded fashion, one assay for each patient. A clinical relapse was defined as an increase by > 1·0 EDSS point. A relative MRI maximum was defined as a time point with > 1 Gd enhancing lesion if preceded and followed by less MRI activity. Serum Il-1ra concentrations were individually defined as extreme (> 3 box lengths from upper boundary) using individual box plots for each patient (box length between 25th and 75th percentile) according to the SPSS procedure "Examine". The association between changes in Il-1ra concentrations and MRI activity was tested with the sign test (increase or decrease of Il-1ra concentration or number of active MRI lesions between two time points).

Relative MRI maxima and clinical relapses were only seen in the group of patients with relapsing-remitting multiple sclerosis, not in the one with chronic-progressive multiple sclerosis. Il-1β was not detectable in serum (n = 118 samples) or CSF (n = 33 samples). Il-1ra could be detected in all serum samples, but not in CSF. Hence serum Il-1ra concentrations were subject to further analysis. The median serum Il-1ra concentrations varied interindividually (range 45–422 pg/ml), but were all within the normal published range.[5] In the patient with the highest total number (64) of Gd enhancing lesions (patient 1), an increase or decrease of MRI activity was followed by an increase or decrease of Il-1ra concentrations by three to four weeks (one time point, $P < 0.05$ in sign test, figure). Individually defined extreme Il-1ra concentrations were only seen in patients with relapsing-remitting multiple sclerosis. There were four such extreme concentrations in four different patients. Two of those coincided with relative maxima of MRI activity, and one with a clinical (spinal) relapse.

Smaller than extreme fluctuations of Il-1ra were not specific for multiple sclerosis activity, as they were also found in the group of patients with chronic-progressive multiple sclerosis without clinical or MRI activity in the observation period. This is probably due to the fact that Il-1 and Il-1ra are involved in a wide range of inflammatory activities.[3] The longitudinal design including monthly visits proved to be essential for defining individual extreme Il-1ra peaks. Because of the few patients, a significant association could be shown in only one patient. In her, the very high disease load (demonstrated by MRI activity) probably allowed us to detect this association. We could not detect Il-1ra in CSF, or Il-1β in CSF or serum, probably because the concentrations were below the detection limit of our ELISA assays. Because the biologically active concentration of Il-1ra is at least one magnitude higher than that of Il-1,[3] Il-1ra may be more easily detectable than Il-1.

In conclusion, we found that fluctuations of Il-1ra may be associated with multiple sclerosis activity. The role of Il-1ra in multiple sclerosis therefore warrants further study.

RAYMOND VOLTZ
MATHIAS HARTMANN
SIMONE SPULER
ANGELA SCHELLER
NORBERT MAI
REINHARD HOHLFELD
Department of Neurology, Klinikum Großhadern, University of Munich and Department of Neuroimmunology, Max-Planck-Institute, Martinsried, Germany
TAREK YOUSRY
Department of Neuroradiology, Klinikum Großhadern, University of Munich

Correspondence to: Dr R Voltz, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York NY 10021, USA.

1 Hohlfeld R, Lucas K, eds. Cytokine networks in multiple sclerosis. *Neurology* 1995;**45** (suppl 6):S1–55.
2 Olsson T. Critical influences of the cytokine orchestration on the outcome of myelin antigen-specific T-cell autoimmunity in experimental autoimmune encephalomyelitis and multiple sclerosis. *Immunol Rev* 1995;**144**: 245–68.
3 Arend WP. Interleukin-1 receptor antagonist. *Adv Immunol* 1993;**54**:167–227.
4 Fisher CJ, Dhainaut JFA, Opal SM, *et al.* Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. *JAMA* 1994;**271**:1836–43.
5 Gruss HJ, Dölken G, Brach MA, Mertelsmann R, Herrmann F. High concentrations of the interleukin-1 receptor antagonist in serum of patients with Hodgkin's disease. *Lancet* 1992;**340**:968.

Pathophysiology of the intermediate syndrome of organophosphorus poisoning

We report a patient with the intermediate syndrome with results of repetitive nerve stimulation studies and single fibre EMG.[1] A hypothesis for the pathophysiology of the intermediate syndrome is proposed.

A 28 year old previously healthy Asian woman drank a bottle of Fenthion (probably about 60 ml). She was admitted swiftly to hospital and treated with gastric lavage and intravenous atropine and a single dose of pralidoxime. After three to four days she developed respiratory weakness and was unable to lift her head. On the fifth day her vital capacity fell. Her facial muscles were weak, as was shoulder abduction and hip flexion. The distal muscles were normal. She had normal reflexes and no sensory deficit. She was intubated, respirated, and atropine was continued.

Her muscle strength slowly improved and she was weaned from the respirator and by the 15th day she was neurologically normal. Neurophysiological studies were carried out on the 7th, 14th, and 18th days. She recovered completely after three weeks. Results from motor and sensory nerve conduction studies on the median nerve on the 18th day were normal.

Repetitive nerve stimulation of the ulnar nerve were carried out at the wrist with recording from the abductor digiti minimi. On day 7 a single stimulus produced a repetitive discharge but the second and subsequent stimuli did not (figure). The repetitive discharge was present at every stimulus with rates at 1/2s but not at 3/s. It was present when the trial stimulus followed a few seconds after tetanus at 20/s for five seconds.

No decremental responses were seen at rates up to 50/s; nor was a decrement present after one minute of exercise or after 10 seconds of repetitive stimulation at 20/s or 50/s. Incremental responses were not seen. Single fibre EMG from the clinically normal extensor digitorum communis showed two single fibre pairs with borderline jitter values; the mean consecutive difference (MCD) was 59 and 63 μs (normal < 55 μs). Frontalis muscle was examined on day 7 and showed increased jitter with blocking. Of 17 fibre pairs, 12 had increased jitter and seven of these had greater than 10% blocking (figure). As expected, blocking was only seen in pairs with a considerably raised MCD.

The intermediate syndrome follows the acute cholinergic crisis of organophosphorus poisoning and is seen in up to 20%–50% of cases depending on the severity of poisoning and duration, and on the type of organophosphorus compound.[1] It differs from myasthenia gravis in that it is a constant rather than progressive weakness, responds adversely to neostigmine, and recovers within 18 days. There are no associated autoimmune phenomena. Decremental responses to repetitive nerve stimulation have been seen sometimes but usually it has been the clinically unaffected peripheral muscles that were studied.

We propose that down regulation of acetylcholine receptors (AChRs) could explain the syndrome and neurophysiological findings. These receptors have a half life of 10 days before undergoing endocytosis and proteolysis within the muscle fibre.[2] Regulation of the number of AChRs and

Multiple sclerosis: longitudinal measurement of interleukin-1 receptor antagonist.

R Voltz, M Hartmann, S Spuler, et al.

J Neurol Neurosurg Psychiatry 1997 62: 200-201
doi: 10.1136/jnnp.62.2.200-b