# LETTERS TO THE EDITOR

In vivo cerebral proton MRS in a case of subacute sclerosing panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a rare encephalopathy caused by persistent defective measles virus in the CNS. Brain lesions may involve all regions of the CNS. The pathophysiological events associated with the disease are characterised by a perivascular infiltration by monocytes and astrocytic proliferation, neuronal degeneration, and demyelination.[1] The exploration of SSPE by brain proton magnetic resonance spectroscopy (MRS) might be of interest to evaluate the extent of the metabolic lesions across the brain. We report here cerebral MRS findings in a 17 year old boy with SSPE.

The first symptoms—difficulties at school—appeared at the age of 16. Six months later, abnormal movements occurred. The symptoms progressed rapidly over the next 2 months with myoclonic jerks and behavioural changes. On admission to the neurological pædiatric unit, the patient presented an inap- propriate gelastic affect with tangential speech but without any temporospatial desorienta- tion. An EEG was characterised by high amplitude slow waves recurring periodically every 4–6 seconds. The patient had had a severe measles infection at the age of 6 months and had been vaccinated against measles at the age of 2. A slight increase in protein con- centration (0.51 g/l) was found in his CSF. Immunoelectrophoresis of CSF showed an inflammatory process with oligoclonal bands. The diagnosis was confirmed by a consider- able increase of specific antimeasles virus antibody in serum and CSF. A decline in clinical status was seen during the 3 weeks in hospital with a vegetative state, decerebrate
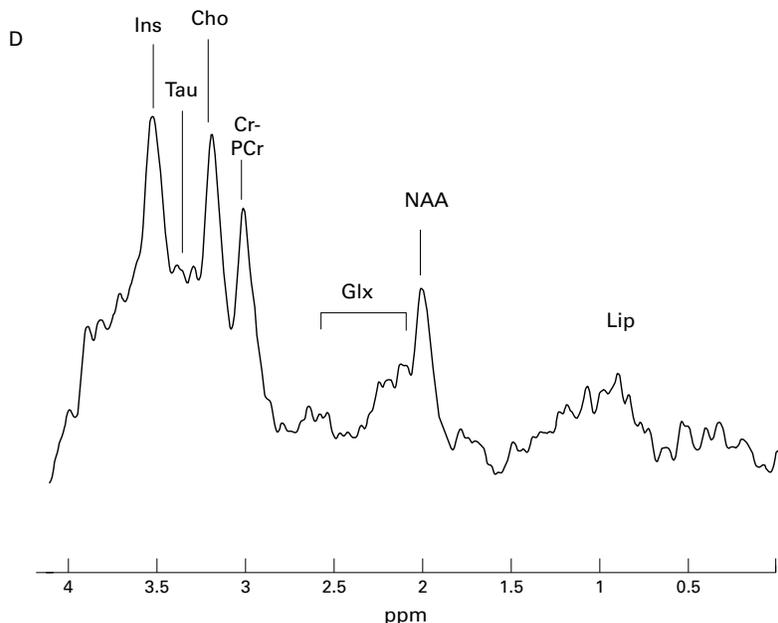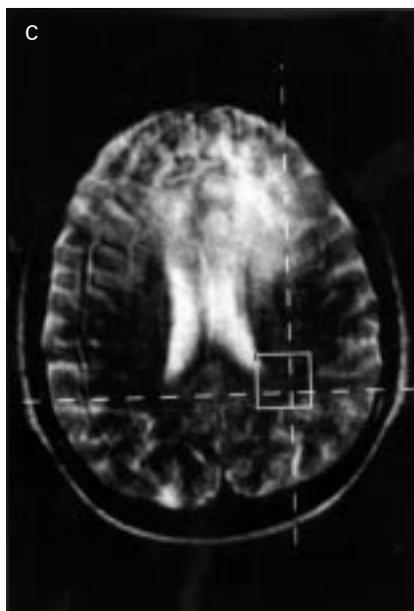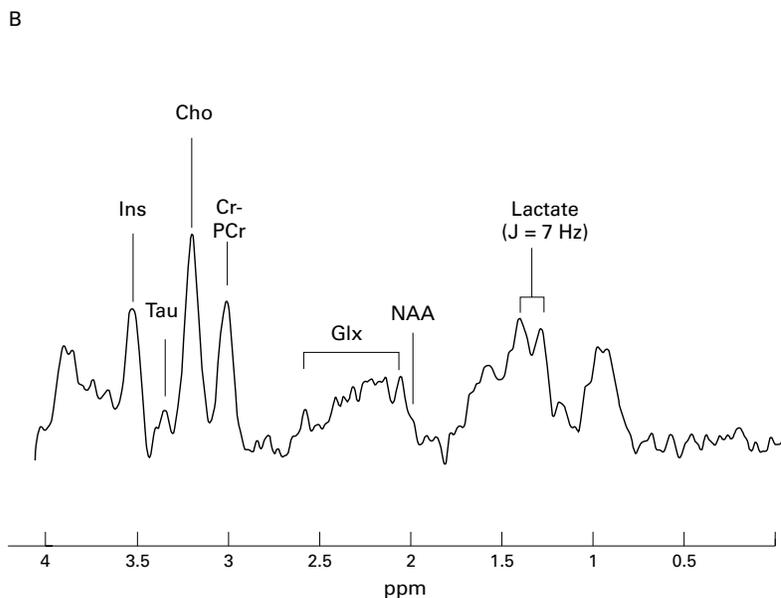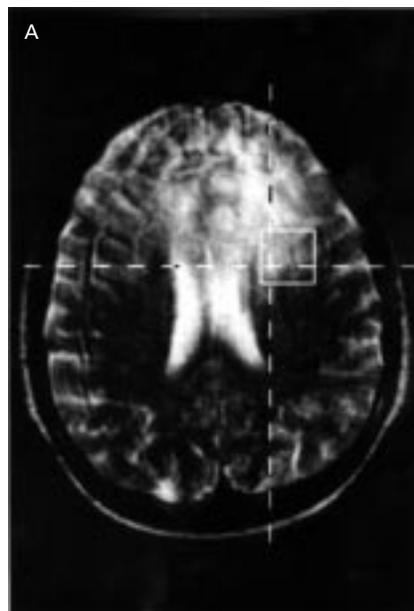
(A and C) Location of the 2 spectroscopic volumes of interest (VOI = 2×2×2 cm) displayed on T2 weighted MRI showing asymmetric frontal white matter hypersignals. (B) Short echo STEAM spectra obtained from the frontal brain lesion and (D) from the parieto-occipital brain lesion in the patient with SSPE. Ins=myoinositol (3.54 ppm), Tau=taurine/scylloinositol (3.33 ppm), Cho=choline containing compounds (3.20 ppm), Cr-PCr=creatine/ phosphocreatine (3.04 ppm), Glx=glutamate-glutamine (2.10–2.45 ppm), NAA=N-acetylaspartate (2.02 ppm), Lip=lipids and/or proteins (between 1.5 and 0.2 ppm).

postures, and impaired respiratory function leading to death. Written informed consent was obtained from the patient's father to perform the MRS examination after standard MRI.

Magnetic resonance studies were performed on a Siemens Magnetom SP63 (Erlangen, Germany) equipped with a 1.5 T magnet at the Timone Hospital in Marseille. Standard MR images were acquired using a T1 weighted FLASH 2D gradient echo sequence (flip angle 90°, TE 10 ms, TR 350 ms, slice thickness 8 mm) in sagittal, coronal, and transverse planes and a T2 weighted turbo spin echo sequence (TPSE: TE=90 ms, TR=3500 ms, slice thickness 5 mm) in the transverse plane. Single voxel proton MR spectroscopy was performed at 63 MHz immediately after standard imaging using the STEAM (stimulated echo acquisition mode, TE/TM/TR = 20/30/1500 ms). Two spectra were acquired from two volumes of interest (VOI = 2 cm×2 cm×2 cm). The first VOI was located in the frontal white matter lesion and the second was located in the parieto-occipital white matter, where there were no apparent lesions (figure A). Spectra were processed using GIFA software (MADelsuc, CBS, Montpellier, France) on a Silicon Graphics Indigo station as previously described.[2]

Brain MRI shows asymmetric and bilateral white matter and cortical lesions in the frontal lobes (figure (A and C)). As presented in the figure (B), the spectrum obtained from the frontal brain lesion of this patient was very abnormal. It was characterised by a dramatic decrease in NAA resonance, an increase in inositol and choline resonances, and the presence of a lactate signal (doublet with 7 Hz J-coupling centred at 1.33±0.02 ppm). Inositol and choline signals were also increased in the parieto-occipital white matter as displayed in the figure (D). Nevertheless, the NAA signal was not reduced. The Glx/S ratio was also decreased in the parieto-occipital VOI. No lactate signal was detected on this spectrum.

The spectrum recorded on frontal white matter displayed severe metabolic anomalies in agreement with the presence of white matter changes found by MRI. Hypotheses can be proposed which relate these metabolic variations to the neuropathological characteristics of the SSPE. Because NAA is a neuronal marker,[3] the large decrease in NAA probably reflects the severe neuronal loss usually found in SSPE. As inositol is a glial cell marker,[3] the increase in the inositol signal can be related to active gliosis. The lack of a mass effect related to œdema suggests that the accumulation of lactate signal shows macrophagic infiltration[3] rather than hypoxic/ischaemic damage. The increase of choline signal might be related either to demyelination or to inflammation.[3] The creatine-phosphocreatine resonance is within normal values suggesting that appreciable necrosis did not occur in this patient.

In the posterior part of the brain, MRI did not display intense white matter lesions, contrasting with the significant metabolic impairment seen by MRS. Although no decrease in NAA was found, the increase in inositol might suggest that glial proliferation takes place before neuronal loss. Regarding the lack of widespread white matter hypersignals on MRI in this region, the rise in choline signal might reflect inflammation rather than demyelination.

These findings show that MRS is better than MRI in showing the diffuse nature of SSPE. In the posterior brain, where MRI lesions are small or absent, severe metabolic alterations take place, involving mainly glial cell activation and inflammatory processes, possibly because of virus reactivation or autoimmune reactions. The presence of MRI lesions in the frontal lobe seems to be associated with major neuronal impairment or loss, in the presence of an active metabolism of glial cells without necrosis.

In conclusion, it could be useful to carry out in vivo brain MRS at the time of MRI examination to evaluate the extent of brain damage in patients with subacute sclerosing panencephalitis.

A M SALVAN
S CONFORT-GOUNY
P J COZZONE
J VION-DURY
Centre de Résonance Magnétique Biologique et Médicale (CRMBM), UMR CNRS 6612, Faculté de Médecine, 27 Bd J. Moulin, 13005 Marseille, France

B CHABROL
J MANCINI
Service de Neuropédiatrie, Hôpital d'Enfants, CHU Timone, Rue St Pierre, 13005 Marseille, France

Correspondence to: Dr Jean Vion-Dury, Centre de Résonance Magnétique Biologique et Médicale (CRMBM), UMR CNRS 6612, Faculté de Médecine, 27 Bd J. Moulin, 13005 Marseille, France. Telephone 0033 4 91 32 42 15; fax 0033 4 91 25 65 39; email viondury@medecine.univ-mrs.fr

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Alternating hemiplegia of childhood or Hashimoto's encephalopathy?

A healthy 14 year old boy had an episode of fever (38.5°C) for 1 day followed, 2 days later, by a progressively worsening confusional state, with slurring of speech, dizziness, and unsteady gait lasting 5 hours. Three months later he had a tonic attack followed by a prolonged postcritical coma which lasted 3 days. On both occasions haematological and biochemical blood tests, brain CT and MRI, CSF examination, and EEG were normal. A few days later, he had another tonic attack of 1 minute, with a confusional state, nominal dysphasia, and left hemiplegia for 8 hours followed by stupor for 3 days. The patient was therefore admitted to our hospital where nominal dysphasia, dystonia, dysmetria, tremulousness, increased deep tendon reflexes, ankle clonus, nystagmus and an enlarged thyroid gland were noted. During his stay in hospital, the patient had a paroxysmal horizontal nystagmus with bilateral mydriasis followed by a tonic attack, involving the right side of the body, with subsequent drowsiness and right hemiplegia for about 10 hours. The next morning he seemed recovered after the nocturnal rest. During that episode several examinations were carried out. EEG recording during wakefulness and spontaneous sleep showed irregular slow waves of 2 Hz–3 Hz on the left frontal region. Brain CT and MRI showed a mild reduction of volume of the left nucleus caudatus, MR angiography was normal. Ictal brain SPECT showed left hemispheric hypoperfusion. Biochemical evaluation encompassing lactate, pyruvate, ketone bodies, amino acids, ammonia, platelets, and protein C and S plasma concentrations performed ictally as well as interictally were normal. Postictal SPECT and EEG performed the next day were normal. A week later, the patient experienced a further tonic attack involving the left side of the body with subsequent drowsiness and left hemiplegia lasting 8 hours, which disappeared after nocturnal rest. EEG recording performed during that episode showed irregular slow waves of 2 Hz–3 Hz on the right hemisphere. Because of the alternating hemiplegic episodes associated with transient hemispheric hypoperfusion, flunarizine (10 mg/day) was administered.

Thyroid function investigation displayed a Hashimoto's thyroiditis, as serum TSH concentration ws 4.8 mUI/l (normal range 0.3–3.1 mUI/l), antithyroglobulin antibodies 1/100 (normal range <1/100), thyroid microsomal antibodies 1:25.600 (normal range <1/100), and TSH receptor antibodies were absent. Serum T3, free T3, T4, and freeT4 concentrations were normal. Flunarizine treatment was maintained for 28 months at the dose of 10 mg/day, and no further clinical relapses occurred during the follow up period. After 8 months, L-thyroxine (50 µg/day) was given in addition to flunarizine because of mild hypothyroidism. Neurological examination and quantitative neuropsychological tests were still normal. The thyroid microsomal antibody concentrations were unchanged at 1/25 600.

Alternating hemiplegia is a main feature of alternating hemiplegia of childhood (AHC), in which multiple paroxysmal manifestations, especially tonic-dystonic attacks, oculomotor disturbances, and the consistent restorative effect of sleep can occur. All these features were present in our patient and AHC was considered as a possible diagnosis. However, we cannot definitely state that the normalisation of the clinical findings after nocturnal rest, which occurred on two occasions in our patient, was related to the restorative effect of sleep or simply appeared during sleep by chance. The appearance of symptoms at the age of 14 years and the absence of mental deterioration were not consistent with AHC.

On the other hand, acute and relapsing neurological symptoms can also occur in patients with Hashimoto's encephalopathy. In our patient the presence of Hashimoto's thyroiditis and a history of a febrile illness just before the onset of the clinical picture manifested by confusional state and coma, are compatible with Hashimoto's encephalopathy. Transient hemiparesis has also been reported in patients with Hashimoto's encephalopathy,[1] however, to our knowledge clear cut transient, recurrent, and alternating hemiplegia episodes restored after sleep have never been reported. EEG findings such as left frontal and right hemispheric slow waves, appearing in our patient during the right and left hemiplegic episodes respectively, and the interictal normalisation are consistent with AHC. However Hashimoto's encephalopathy

cannot be ruled out as generalised or focal slow waves on the EEG have been reported.[2] Brain SPECT, performed in our patient during a right hemiplegic attack, showed a left hemispheric hypoperfusion, which was completely resolved interictally. These findings are characteristic of AHC. On the other hand, brain SPECT has been reported in only a few cases of Hashimoto's encephalopathy, showing global decreased perfusion restored during clinical improvement in a patient,[3] and left temporal hypoperfusion in another patient.[4] Therefore, as proposed by Forchetti *et al*[3] in patients with Hashimoto's encephalopathy, we might hypothesise that a possible autoimmune mechanism causes an alteration in the vascular reactivity of the cerebral microvasculature inducing a reduction of blood flow that in our patient was prevalent in one or in the other hemisphere alternatively. With respect to the treatment, flunarizine is the elective drug in AHC, even if it is only able to reduce the long lasting nature and the severity of the attacks; it does not influence their frequency. A rapid control of symptoms, as in our patient, was therefore unexpected. To our knowledge, there are no reports on Hashimoto's encephalopathy treated with flunarizine, even if a favourable effect of the drug on decreased brain blood flow might be expected, considering the positive results obtained in migraine and peripheral vascular disorders. In our patient, L-thyroxine was administered 8 months after flunarizine monotherapy, therefore it did not influence the neurological picture. Assuming that our patient is really affected by Hashimoto's encephalopathy, we have to admit that flunarizine is effective in this condition. In patients with Hashimoto's encephalopathy corticosteroids are considered the elective drugs. However, reoccurrence of symptoms when the corticosteroids are withdrawn or even while taking them and their inability to prevent mental deterioration in some cases have been reported.[5] For these reasons, the possibility of using another effective drug such as flunarizine in Hashimoto's encephalopathy would be of paramount importance, because it has fewer side effects and can be administered continuously.

In conclusion we think that our patient has an unusual form of Hashimoto's encephalopathy, even if an atypical AHC associated with Hashimoto's thyroiditis by chance cannot be theoretically ruled out. Therefore, we should consider the effectiveness of flunarizine therapy, that will have to be validated further in patients with Hashimoto's encephalopathy in whom a decreased brain perfusion is documented.

PAOLO BALESTRI
SALVATORE GROSSO
GIANLUCA GARIBALDI
*Institute of Clinical Paediatrics, University of Siena,
Siena, Italy*

Correspondence to: Dr Paolo Balestri, Institute of Clinical Paediatrics, Viale Bracci, Le Scotte, 53100 Siena, Italy. Telehone 0039 577 586522; fax 0039 577 586143; email balestri@unisi.it

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Subthalamic nucleus stimulation improves directly levodopa induced dyskinesias in Parkinson's disease

Bilateral chronic subthalamic nucleus (STN) stimulation is a new and useful surgical method to improve parkinsonian disability. The improvement involves all the major parkinsonian signs.[1] Recently, Krack *et al*[2] reported that chronic stimulation of the STN also improved levodopa induced dyskinesias, although they explained this effect mainly by a decrease in the levodopa dosage. We report on a patient who presented a marked improvement of levodopa induced dyskinesias without decreasing the daily dosage of levodopa.

A 68 year old man was diagnosed with Parkinson's disease at the age of 38, and started levodopa at the age of 43, with good initial effect. At the age of 56 he developed a peak of dose choreiform dyskinesias in the trunk and limbs and 2 years later he also had motor fluctuations of the wearing off type. Since 1993, the patient had severe generalised choreiform dyskinesias that were present for about 75% of the diurnal time. Presurgery treatment included benserazide/levodopa (50/200 mg five times a day), plus selegiline
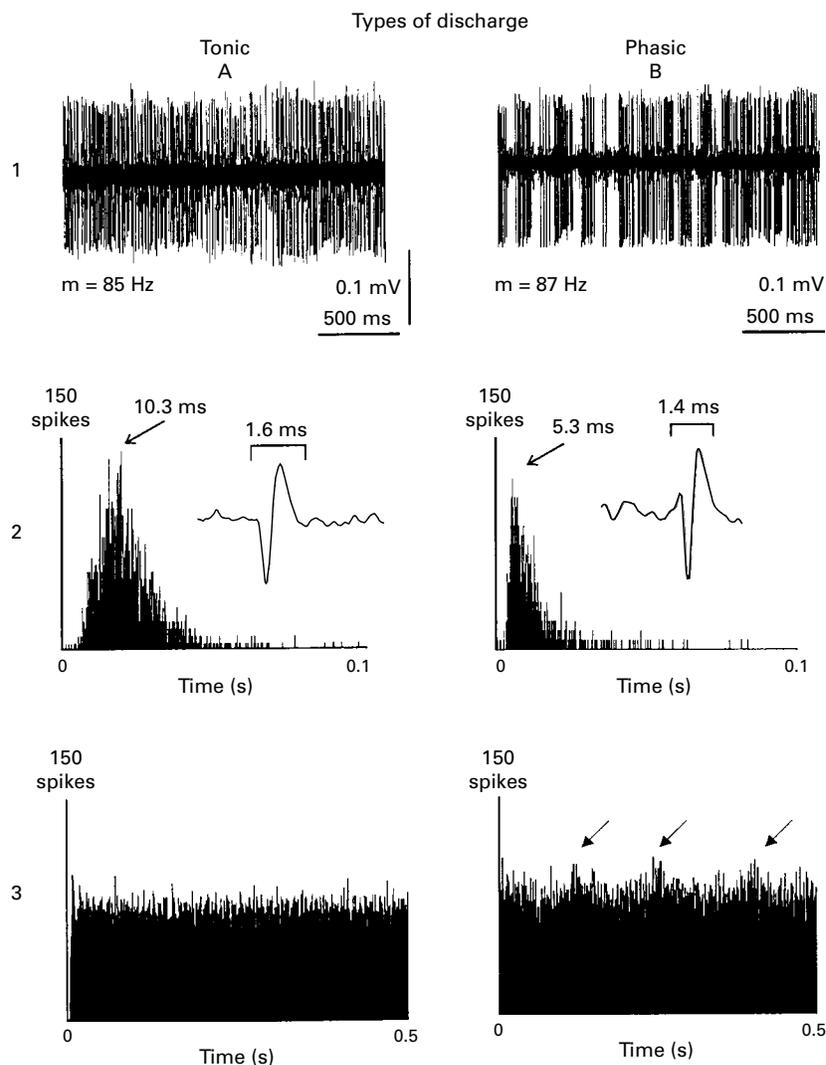
Intraoperative neurophysiological recording. Two types of cell discharges were recorded. (A) Tonic neuron: A1, raw data as recorded in the operating theatre of a subthalamic cell, it discharges in a regular pattern (tonic) at high frequency (mean=85 Hz): discharges are subsequently changed into events to be analysed (A2–A3); A2, interval histogram, a symmetric frequency distribution can be seen with the highest peak at 10.3 ms, the insert shows only one action potential of the same cell (negative downwards); A3, autocorrelation histogram made with every action potential to show the type of cell's activity. The flat outline indicates a great regularity in the firing. (B) Phasic neuron. B1, raw data, as recorded in the operating theatre, of a different type of subthalamic cell, it discharges irregularly at high frequency (mean=87 Hz) with bursts formed by several action potentials subsequently changed into events for statistical analysis (B2-B3); B2, interval histogram. It displays a different outline distribution than the tonic cell with the highest peak at 5.3 ms corresponding to the time interval found when discharging in burst mode, the insert illustrates only one action potential of the same cell with a total duration of 1.4 ms; B3, autocorrelation histogram. The cell shows a tendency to discharge in bursts as seen by the waves (arrows) consisting in periodic increments and decrements in the discharge rate reaching a rhythmical activity of 6–7 Hz.

(10 mg/day). The motor score of the unified Parkinson's disease rating scale (UPDRS) in the off condition was 51, and in the on condition, 37. The dyskinesia score (six body parts, each scored 0–4, maximum score 24)[1] in the on condition was 15. The patient was operated on bilaterally in the STN according to the method of Limousin *et al*[1] with slight modifications, using neurophysiological recording (figure). Antiparkinsonian therapy was initially maintained. Three months after surgery, the motor score of the UPDRS in the off condition was 48, and in the on condition 36, when the stimulation was off; and improved to 37 and 22, respectively, when the stimulation was switched on. The patient had mild dyskinesias in the lower limbs for no more than 10% of the diurnal time. The dyskinesia score was assessed during the maximum motor response to a single morning dose of 50/200 mg benserazide/levodopa. Ten hours before this levodopa test, the stimulation was switched off, and the patient kept off levodopa. The dyskinesia score was 15 when the stimulation was off, and lessened immediately to 2 when the stimulation was switched on.

Unilateral STN stimulation induces hemiballism in healthy monkeys[3] and improves all parkinsonian symptoms,[1] including levodopa induced dyskinesias, in patients with Parkinson's disease.[2] Although the improvement of levodopa induced dyskinesias has been attributed by Krack *et al*[2] to the decrease of levodopa dosage, our patient showed a marked improvement after surgery despite the fact that the levodopa dose could not be decreased after optimising the antiparkinsonian therapy. The improvement of levodopa induced dyskinesias in our patient occurred both during activities of daily living and after a levodopa acute test. To minimise a possible maintained effect of the subthalamic STN stimulation, which hypothetically could have changed the dyskinesia threshold, the patient was in off drug and off stimulation conditions 10 hours before the levodopa acute test. Levodopa elicited a severe peak of dose dyskinesias that were relieved immediately when the STN stimulation was switched on. These data suggest that the effect of STN stimulation is different in healthy monkeys[3] compared with parkinsonian patients with levodopa induced dyskinesias, and suggest that the improvement of levodopa induced dyskinesias could be related directly to the effect of STN stimulation.

ROBERTO FIGUEIRAS-MÉNDEZ
Unit of Functional Neurosurgery, Clínica Nuestra Señora del Rosario, Madrid, Spain
Department of Neurosurgery, Centro Especial Ramón y Cajal, Madrid, Spain

FERNANDO MARÍN-ZARZA
Unit of Functional Neurosurgery, Clínica Nuestra Señora del Rosario, Madrid, Spain

JOSÉ ANTONIO MOLINA
Department of Neurology, Hospital Universitario Doce de Octubre, Madrid, Spain

FÉLIX JAVIER JIMÉNEZ-JIMÉNEZ
MIGUEL ORTÍ-PAREJA
Hospital "Príncipe de Asturias", Universidad de Alcalá de Henares, Madrid, Spain

CARLOS MAGARIÑOS
Unit of Neurophysiology

MIGUEL ANGEL LÓPEZ-PINO
VICENTE MARTÍNEZ
Unit of Radiology, Clínica Nuestra Señora del Rosario, Madrid, Spain

Correspondence to: Dr Félix Javier Jiménez-Jiménez, C/Corregidor José de Pasamonte 24, 3º D, E-28030 Madrid, Spain. Telephone 0034 91 4376078; fax 0034 91 3280704; email Fjimenezj@meditex.es

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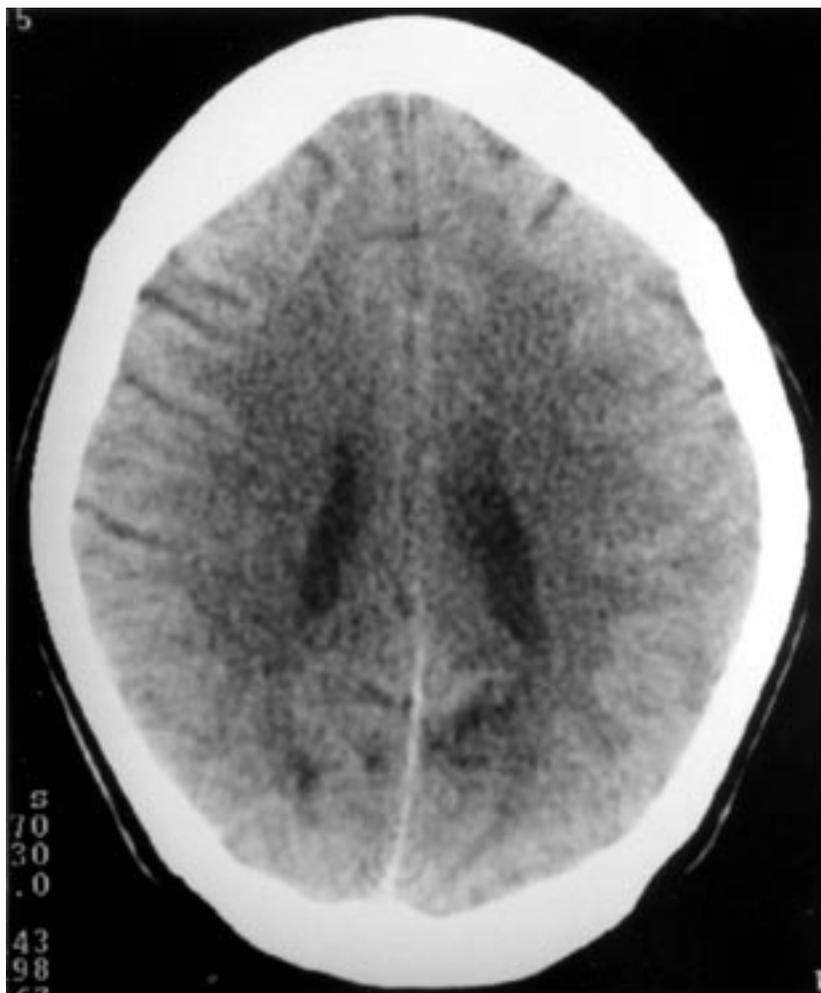## Cerebral infarction: a rare complication of wasp sting

It is stated that four people die in the United Kingdom every year from anaphylactic reactions to wasp and bee stings.[1] However, long term sequelae, including neurological complications, are rare. We report on a young woman who sustained a stroke after a wasp sting and review the literature with particular reference to possible underlying mechanisms of stroke.

A 30 year old woman was seen in a casualty department, 45 minutes after a wasp sting on her left arm. She complained of immediate localised itch, followed by facial and arm swelling and widespread pruritis. She was noted to have a normal conscious level and widespread urticaria and her blood pressure at admission was 90/50. An intravenous infusion of gelofusine was started and she was given subcutaneous adrenaline (1 mg), intravenous hydrocortisone (100 mg), and intramuscular chlorpheniramine (10 mg). Her blood pressure responded and she had no further recorded hypotension. However, after infusion of gelofusine (3 l) over 2 hours she developed respiratory distress and hypoxia. Examination and a chest radiograph showed acute pulmonary oedema and she was intubated and ventilated for 36 hours. She received intravenous frusemide (150 mg in total over 8 hours), but did not require inotropic support. Chlorpheniramine (10 mg thrice daily) and hydrocortisone (100 mg thrice daily) were continued for 48 hours. After extubation she complained of difficulty seeing objects in her right upper visual field and a right homonymous quadrantinopia was demonstrated. Brain CT showed a left occipital infarct (figure).

She subsequently made a full recovery from the quadrantinopia. She was shown to have IgE antibodies to both wasp and bee venom and a positive skin test to wasp venom and underwent successful desensitisation to wasp venom.

Cerebral infarction in this woman occurred in the setting of anaphylaxis to a wasp sting. There was only a single recorded episode of hypotension which was rapidly corrected and was not thought to be sufficient to cause her stroke. The infarct was an occipital cortical lesion and not in a typical border zone distribution.

Computerised tomogram showing left occipital infarct.

Vascular complications of bee and wasp stings are rare. Cerebral infarction has only been reported in three other people.[2 3] In one three wasp stings were followed by collapse and a tonic-clonic seizure. Hypotension was not recorded. He was treated with adrenaline, barbiturates, and steroids. It is unclear whether the development of a hemiparesis preceded or followed this treatment. Brain CT confirmed cerebral infarction. Both other patients died after bee or wasp stings. At postmortem cerebral infarction was found in both.[3] The mechanism of cerebral infarction was not alluded to.

Acute myocardial infarction has been reported four times.[4] It has been suggested that this may be due to a combination of coronary vasoconstriction secondary to mediators released after wasp sting, aggravated by exogenous adrenaline given as part of the treatment and by platelet aggregation.[4 5] It is likely that the mechanism of cerebral infarction in this patient was similar. Wasp venom contains vasoactive, inflammatory, and thrombogenic peptides and amines, including histamine, leucotrienes, and thromboxane. The venom also contains allergenic proteins such as phospholipases which elicit an IgE response, resulting in mast cell activation.[6] Mast cell activation results in release of preformed substances such as histamine as well as de novo synthesis of other mediators. Constriction of coronary arteries has been shown to occur in response to histamine.[7] Both thromboxane and leucotrienes have been shown to be vasoconstrictors.[8] The adrenaline that the patient was given may also have been implicated in vasoconstriction, resulting in her cerebral infarct. Many of the factors released, including thromboxane and leucotrienes, cause platelet aggregation resulting in a prothrombotic state.

The other neurological complications of stings which have been reported are individual cases of ocular myasthenia gravis,[9] optic neuritis, limb numbness, and trigeminal neuralgia[10] and three cases of encephalopathy, one of which was fatal.[11] Postulated mechanisms include both a toxic effect of venom[9] and hypersensitivity to venom.[10 11]

FRANCESCA CRAWLEY
FRED SCHON
Department of Neurology, Atkinson Morley's Hospital, London, UK

MARTIN M BROWN
Division of Clinical Neuroscience, St George's Hospital Medical School, London, UK

Correspondence to: Dr Fred Schon, Consultant Neurologist, Atkinson Morley's Hospital, London SW20, UK

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Cerebrospinal fluid manganese concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI

Recently, there have been some reports that MRI shows characteristic brain lesions in patients with parenteral nutrition containing manganese (Mn), or hepatic failure, and that the serum or whole blood Mn concentration is often increased.[1–3] T1 weighted MRI in these patients has shown hyperintensity, always in the bilateral globus pallidus and sometimes in part of the brainstem, although no abnormalities have been found on T2 weighted MRI. The Mn concentrations of CSF in these patients, however, have not been previously measured, because values in control subjects were previously undetermined. The present study was designed to investigate the CSF Mn concentrations in control subjects, and to evaluate the concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI.

We examined five patients with the appropriate hyperintensity on T1 weighted MRI, aged from 31 to 72 years (mean 55.8 (SD 16.9) years); two with parenteral nutrition containing Mn (patients 1 and 2), two with Child's grade B cirrhosis (patients 3 and 5), and one without any specific factors relating to Mn or hepatic failure (patient 4, who had parkinsonism). In addition, we investigated 10 age matched control subjects without hyperintensity, aged from 28 to 78 years (mean 54.2 (SD 15.9) years) (table). The MRI was performed on a 1.5 Tesla magnet. In all five patients, T1 weighted MRI in the patients showed hyperintensity in the bilateral globus pallidus and in the region of the substantia nigra or the quadrigeminal plate, although T2 weighted MRI and brain CT showed no abnormalities. Ten control subjects from the neurology and psychiatry service with no history of parenteral nutrition containing Mn, or hepatic failure, showed no abnormal findings on T1 weighted MRI. We obtained blood and CSF samples from the five patients and 10 control subjects with informed consent. The serum, whole blood, and CSF Mn concentrations were measured by a standard method using graphite furnace atomic absorption spectrometry (Model VARIAN SPECTRA A-40) within 1 month after recognition of the symmetric pallidal hyperintensities. The CSF Mn concentrations were measured by diluting the sample with 0.5% (v/v) nitric acid to yield absorbance values within the linear range and injecting 200 µl into the furnace. The mean serum, whole blood and CSF Mn concentrations were calculated for the patients and control subjects. The non-parametric Mann-Whitney U test was used to assess the significance of differences between the two groups.

The serum, whole blood and CSF Mn concentrations of the patients and control subjects are listed in the table. All the serum and whole blood concentrations of the control group were within the normal range, and their CSF concentrations were mean 0.47 (SD 0.25)µg/l, a relatively narrow range. The CSF Mn concentration (2.1 µg/l) of patient 4, which was the lowest in the patient group, was much higher than 2 SD above the mean of the control group, but the serum Mn concentration of patient 4 and the whole blood Mn concentrations of patients 1, 3, and 4 were all within the normal range. The serum and CSF Mn concentrations of the patient group were significantly higher (p=0.023 and p=0.002 respectively) than

Serum, whole blood, and CSF Mn concentrations in five patients with hyperintensity on T1 weighted MRI and 10 control subjects without hyperintensity

	Age (y)	Sex	Primary disease (parenteral Mn dose (mg/day)/duration (days))	Serum Mn (µg/l)	Whole blood Mn (µg/dl)	CSF Mn (µg/l)
Patients:						
1	31	F	Pylonephritis (1.1/20)	1.7	1.6	6.7
2	46	F	Wernicke's encephalopathy (1.1/51)	2.1	4.4	3.8
2	64	M	Child's grade B cirrhosis	2.2	2.4	3.0
4	66	M	Parkinsonian syndrome	1.2	1.6	2.1
5	72	F	Child's grade B cirrhosis	2.3	4.2	3.1
Mean (SD)	55.8 (16.9)			1.90 (0.45)	2.84 (1.37)	3.74 (1.76)
Control subjects:						
1	28	F	Acute disseminated encephalomyelitis	1.5	1.7	0.7
2	40	M	Chorea-acanthocytosis	1.5	2.0	0.9
3	43	M	Multiple sclerosis	1.3	1.7	0.2
4	45	F	Neurosis	0.9	1.0	0.6
5	49	M	Guillain-Barré syndrome	1.9	2.0	0.4
6	57	F	Parkinsonian syndrome	1.0	1.3	0.6
7	61	F	Malignant syndrome	0.8	1.4	0.2
8	70	M	Progressive supranuclear palsy	0.9	1.1	0.3
9	71	M	Progressive supranuclear palsy	1.2	1.5	0.6
10	78	M	Parkinson's disease	1.3	2.8	0.2
Mean (SD)	54.2 (15.9)			1.23 (0.34)	1.64 (0.53)	0.47 (0.25)

Normal ranges: serum Mn 0.2-1.6µg/l; whole blood Mn 1.3-3.1µg/dl; CSF Mn concentrations have not been determined.

those of the control group, whereas the whole blood Mn concentrations were not significantly different (p=0.086) between the two groups.

This is the first study to evaluate the CSF Mn concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Hyperintensity on T1 weighted MRI is associated with many factors, including calcification, lipid, haemorrhage, and Mn, but the pattern of MRI abnormalities in all the five patients was identical with that seen because of Mn deposition and the serum or whole blood Mn concentrations were often increased.[1–3] In the blood, Mn can bind to transferrin in the trivalent state and to albumin or α2-macroglobulin or low weight solutes in the divalent state. The blood Mn is transferred to the brain through the blood-brain barrier by several transport systems.[4] Recently, increased Mn concentrations were recognised in postmortem tissue samples from the brains of patients with long term parenteral nutrition containing Mn, or severe cirrhosis.[2 5] From our study, the CSF Mn concentrations were increased more than those in serum and whole blood in all patients and, in particular, patient 4, who had no parenteral nutrition or hepatic failure, showed an increase only in CSF Mn concentration. The CSF Mn concentrations are considered to reflect the accumulation of Mn in the brain tissue most directly of the three Mn concentrations. The reason why patient 4 is connected with Mn may be individual susceptibility.[6] Moreover, Mn neurotoxicity caused neuropsychiatric symptoms including pyramidal and extrapyramidal signs.[1–3] The findings suggest that a high degree of correlation exists between hyperintensity and the CSF Mn concentration, and that the increase may be a most useful marker and predictor of Mn neurotoxicity in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Further studies with more patients are necessary to elucidate a precise correlation between Mn neurotoxicity and the CSF Mn concentration.

T KATSURAGI
E ISEKI
K KOSAKA
Department of Psychiatry, Yokohama City University School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236–0004, Japan

S KOYANO
K IWABUCHI
Department of Neurology and Psychiatry, Kanagawa-ken Rehabilitation Center, 516 Nanasawa, Atsugi, Kanagawa 243–0121, Japan

Correspondence to: Dr T Katsuragi, Department of Psychiatry, Yokohama City University School of Medicine, 3–9 Fukuura, Kanazawa-ku, Yokohama 236–0004, Japan. Telephone 0081 45 787 2667; fax 0081 45 783 2540; email tk8041@med.yokohama-cu.ac.jp

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CORRESPONDENCE

The role of the nucleus intercalatus in vertical gaze holding

I was interested to read the report of Janssen *et al*[1] of a patient with upbeat nystagmus who had had a medial medullary infarct. By contrast with our patient,[2] their patient had slow phases with a constant velocity, a "vestibular" type of nystagmus of central origin. As noted by Janssen *et al*, Hirose *et al*[3] have reported on a patient with a medial medullary infarct and upbeat nystagmus; some slow phases were exponential, some of constant velocity.

In the analysis of slow phases it is useful to plot eye velocity against position rather than plot eye position against time. In this representation, the plot of a vestibular type of slow phase with constant velocity is a horizontal straight line. However, when position varies exponentially with time, velocity is a linear function of position:

$$dx/dt = -kx, \quad x = x_0 \exp(-kt)$$

The gradient k is the decay constant. A regression line may be fitted and confidence limits for k established. A more detailed analysis[4] of the upbeat nystagmus in our patient with a medial medullary infarct confirmed that decay constants were significantly different from zero and therefore not "vestibular". However, the decay constants for the different slow phases varied and the plot of eye velocity against position seemed to be non-linear (figure). It is not surprising slow phases attributable to "integrator failure" might not be strictly exponential. The model of the perihypoglossal nuclei as a pure integrator rests on the assumption that the statics of the eye (the oculomotor plant) can be modelled by a pure "spring and dashpot",
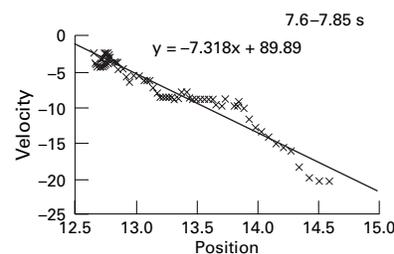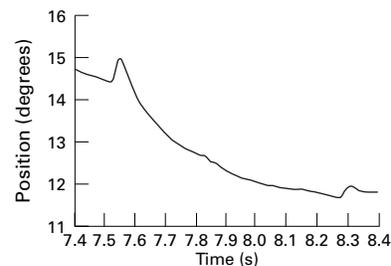
Position-time and velocity-position plots of the slow phase of a vertical nystagmoid jerk.

second order linear differential equation.[5] This is an approximation for horizontal movements and a greater approximation for vertical eye movements. It also rests on the assumption that the anatomical connections are more simple than in reality. The variability of decay constants is consistent with the findings of Hirose *et al*.[3] This may reflect the varying activity of other afferents to the perihypoglossal nuclei. Nevertheless, the approximate linearity of the plots suggest that part of the function of the nucleus intercalatus, the most caudal of the perihypoglossal nuclei, is integration. Perhaps the reason that such a caudal structure may be involved in vertical integration is the need to coordinate vertical head position signals from cervical afferents with integrated head velocity signals from vestibular nuclei.

It would be of interest to know whether velocity–position plots of any of the slow phases of the patient of Janssen *et al*[1] show a non-zero gradient.

N A R MUNRO
Department of Neurology, King's Healthcare Trust, Mapother House, Decrispigny Park, London SE5 8AZ, UK

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Bronstein et al reply:

We thank Munro for his interest in the patient we reported in this *Journal* with a low medullary lesion and upbeat nystagmus.[1] The lesion probably involved the nucleus intercalatus, the lowermost part of the perihypoglossal nucleus, a nucleus thought to perform integration of ocular-motor signals. For the benefit of the general readership of this *Journal* we should like to clarify that the integration alluded to is mathematical integration. For instance, eye or head velocity signals arriving at such an integrator emerge as approximations of eye or head position signals. Currently accepted theories of ocular-motor function establish that a lesion to a gaze holding integrator produces nystagmus with slow phase velocity showing exponential decay. By contrast, peripheral vestibular lesions cause nystagmus with linear (constant) slow phase velocity.

The current discussion is centred on the findings in three recently reported patients with lesions probably involving the nucleus intercalatus.[1–3] The patients reported by Munro *et al*[2] and Hirose *et al*,[3] with large medullary lesions, had predominantly exponentially decaying slow phase velocity. Our patient, with a small paramedian lesion, had nystagmus with linearly decaying slow phase velocity.[1] Following Munro's suggestion we obtained velocity-position plots of single nystagmic beats and found most of them to be linear (horizontal line on velocity-position
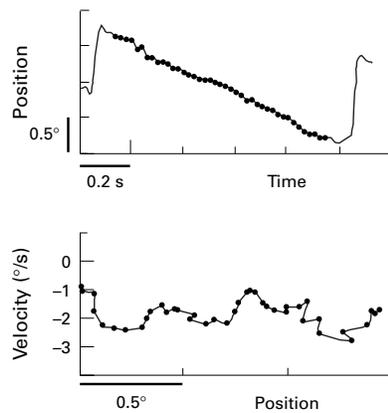
Position v time and velocity v position plots of a single nystagmic beat in the patient described by Janssen et al.[1]

plots (figure)). Only about 10%-15% of nystagmic beats showed some degree of exponential decay (velocity-position plots with a non-zero gradient). On this basis, as well as on the presence of tilt (otolith) stimulus sensitivity, we argue that a small nucleus intercalatus lesion presents clinically as a central vestibular nystagmus. Larger lesions may damage additional neuronal circuits involved in ocular-motor integration.[4]

A M BRONSTEIN
A J LARNER
J C JANSSEN
S F FARMER
National Hospital for Neurology and Neurosurgery, Queen Square, London, UK

1 Janssen JC, Larner AJ, Morris H, *et al*. Upbeat nystagmus: clinico-anatomical correlation. *J Neurol Neurosurg Psychiatry* 1998;**65**:380–1.
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"Summary measure" statistic for assessing the outcome of treatment trials in relapsing-remitting multiple sclerosis

In response to the recently published paper by Liu *et al*,[1] we wish to initiate further discussion regarding the proposed area under the curve (AUC) summary measure and comment on some inherent difficulties with this method.

In the paper, Liu *et al* note that when constructing the summary AUC, the "essential components are the sets of serial impairment or disability data, preferably with frequent sampling points for each patient..." This is in fact a crucial point and depending on the schedule of observations, the observed plot of the expanded disability status scale (EDSS) over time can look quite different from the true curve. For example, consider figure D that has been reproduced below from the paper (figure A). This plot of EDSS over time represents a continuum, which in reality is unlikely to be fully observed as patients are not seen on a daily or weekly basis throughout a study because it is not practical to do so. Instead, patients are scheduled to return for assessment at certain times during the study.

If, hypothetically, this patient was seen every 3 months by the study investigator, the observed plot of EDSS over time would appear as figure B. However, if this patient was seen every 6 months during the study instead, the observed plot of EDSS over time would appear as figure C. These two "observed" EDSS curves look different, even though they represent the same underlying curve. It is obvious that the resulting AUC for each plot would also differ in magnitude. If patients could be measured daily to create a smooth, accurate curve, this would not be an issue. In practice, the resulting EDSS curve over time is spiky and uneven and so the AUC measurement is greatly impacted.

It is also necessary to clarify what the proposed AUC summary measure is actually measuring and how it can be interpreted. The interpretation can vary depending on such factors as how baseline values were handled in the calculation of the AUC, whether unscheduled visits were included, and which summary statistics are reported. For example, if scores are "normalised to baseline" as described in the article, patients with completely different baseline EDSS scores can have the same AUC, yet the degree of disability will be greater for the patient with the higher baseline EDSS. From a clinical perspective, the question should be raised, "Do we want to consider the disability of these patients to be the same by using the AUC summary measure?" Likewise, as the article points out, "Caution is necessary in short trials of 2 or 3 years, as fixed neurological deficits are accumulating very slowly, and an increased AUC at the end of a trial may simply represent transient disability which has either resolved or has yet to resolve." This implies that the AUC summary measure may not be a good indication of irreversible clinical deterioration. The AUC measure may reflect exacerbations rather than sustained disability.
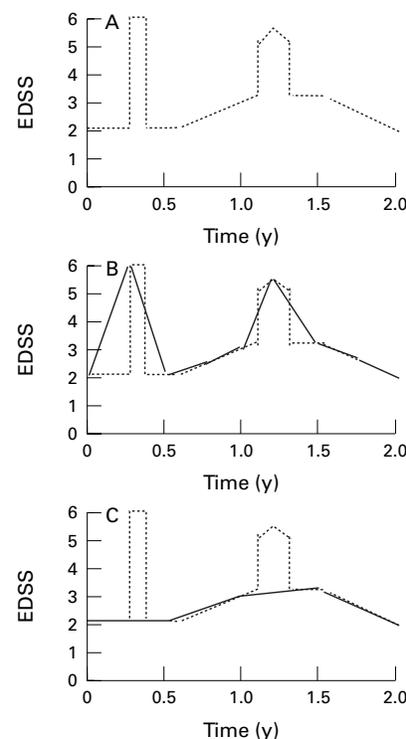
The concept of AUC has been used extensively in other fields with great success. Most commonly, it has been used when measuring either peaked data (outcome variable starts from a baseline, rises to a peak, and then returns to baseline) or growth data (outcome variable steadily increases or decreases with time and does not start to return to its initial value over the period of the study).[2] Even then, however, AUC is not used in isolation. For example, when used in pharmacokinetic modelling of blood concentration data, the maximum concentration and the time to maximum concentration are also reported. This is because the AUC alone cannot summarise the *shape* of the curve. We think that irreversible disability progression in multiple sclerosis must continue to be measured by time to event and intrapatient changes in disability. Improvements in assessment of disability are more likely to come from outcome measures such as the multiple sclerosis functional composite[3] that overcome issues with the EDSS such as non-linearity.

NANCY A SIMONIAN
ARTHUR MCALLISTER
JULIA LULL
Biogen, 14 Cambridge Center, Cambridge, MA 02142, USA

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Liu et al reply:

We welcome the opportunity to discuss the role of the AUC (area under the plotted curve of disability against time) as a summary measure statistic in treatment trials of multiple sclerosis, although many of the points raised by Simonian and her colleagues simply reiterate those we made in our paper.[1]

The first comment considers the impact of the number of points on the shape of the disability curve. We agree that the sampling frequency will alter the shape of the curve and this is precisely why the AUC method is preferable to the conventional approach, which emphasises single or two point assessments. By taking account of data from all the assessment points, the bias highlighted in figures B and C by Simonian *et al* would have a greater chance of averaging out. Obviously, the greater the sampling frequency, the better the approximation to the disability actually experienced (figure A). For pragmatic reasons, in practice, the number of assessments are limited. Trials with a scheduled visit frequency of only 6 months[2 3] will necessarily be less accurate in following actual in trial disability than those with higher rates of assessment[4–6] *whatever the clinical rating scale tool used.* Our approach takes account of this fact.

On the important question of clinical interpretation of the AUC summary measure, we reiterate our argument that the AUC provides an index of in trial morbidity, or as we called it, "total disability experience" (summed transient and irreversible disability). This is clinically meaningful and relevant in short studies involving relapsing-remitting multiple sclerosis, in which many disability

changes which impact patients' daily lives, remit before the end of a trial.

The problem of summating estimated disability changes at different levels of clinical rating scales as raised by Simonian and colleagues, is a different point altogether and hardly limited to an analysis by the AUC statistic. If data on changes at different levels of a rating scale are required, then stratification analysis according to baseline disability[7] can be carried out using any outcome measure including "confirmed progression", overall EDSS change, or AUC.

Simonian and colleagues consider that AUC is appropriate for "growth data", which in terms of multiple sclerosis would apply to patients deteriorating steadily with chronic progressive disease. In fact, as stated by Matthews *et al*,[8] the AUC statistic is particularly relevant for summarising *peak data* such as the increase and decrease of disability associated with a relapse. However, it is also relevant and appropriate for the analysis of the complex mixture of peaked, multipeaked, and growth data, which characterises the disability course of relapsing-remitting multiple sclerosis. If the functional form of the disability progression were known, we would of course be able to use parametric modelling (for example, exponential decay or linear decay). Our analysis is non-parametric and the only assumptions we make are that the events are stochastic and the measurements are serially correlated.

We did not imply that the AUC statistic "should be used in isolation" any more than a mean or median EDSS should be the only summary measure. The AUC clearly does not provide information about the direction of disability change and we pointed out that additional analyses would be necessary to determine time trends. Whereas we agree that theoretically, *irreversible disability progression* in multiple sclerosis is best assessed by time to events, in practice outcomes such as EDSS of 6.0, are not truly irreversible and subject to substantial measurement error. Event history analysis is more appropriate for truly irreversible events such as death or loss of virginity (!) rather than those we typically use in relapsing-remitting multiple sclerosis. Commonly employed disability end points, such as EDSS change from study entry to completion, and the so-called confirmed progression at 3 or 6 months, have major flaws as already discussed in our paper.

The relative merits of clinical rating scales such as the EDSS, Scripps neurologic rating scale, or the proposed multiple sclerosis functional composite should not be confused with the statistical methods used to analyse serial scores acquired from these scales. Whether the functional composite turns out to be better or worse than established scales remains to be seen, but this does not in any way impinge on the desirability of applying AUC analysis to serial data derived from any clinical rating scale (including the functional composite). We think that because this summary measure statistic (AUC) takes into account both transient and permanent disability, as well as the magnitude and duration of disability changes, and because it is simple to apply, sensitive and variance stabilising through its incorporation of all serial time points, it is both appropriate and clinically meaningful for outcome analysis of treatment trials of relapsing-remitting multiple sclerosis.

CLARENCE LIU
LANCE D BLUMHARDT
Division of Clinical Neurology, Faculty of Medicine, University Hospital Queen's Medical Centre, Nottingham NG7 2UH, UK

ALAIN LI WAN PO
Department of Pharmaceutical Sciences, Aston University, Birmingham B4 7ET, UK

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Hypothesis on the pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS

We read with extreme interest the article by Tan and Guiloff.[1] The excellent review illustrates the current knowledge on transmethylation abnormalities in the pathogenesis of neurological complications of HIV infection. It is most convincing in its ability to bridge evidence of cytokine activation, myelinotoxic, and neurotoxic events, with abnormalities of methylation in the nervous system.

Our group has been working for years on the hypothesis that AIDS associated myelopathy and other HIV related neurological disorders are consequent to an induced metabolic abnormality of the transmethylation pathway. Our initial clinical studies with methionine supplementation suggest that signs and symptoms of myelopathy and cognitive function improve with methionine supplementation.[2–5] Although still preliminary, these data offer further argument for a pathogenetic role of methylation in neurological complications of AIDS, and suggest that a therapeutic approach aimed at correcting this metabolic abnormality may be beneficial. We are now conducted a larger, controlled study to further assess treatment of neurological complications of AIDS with L-methionine.

ALESSANDRO DI ROCCO
PETER WERNER
Department of Neurology, Beth Israel Medical Center and Albert Einstein College of Medicine, New York, USA

Correspondence to: Dr A Di Rocco, Beth Israel Medical Center, PACC, 10 Union Square east, Department of Neurology, New York, NY 10003, USA.

1 Tan SV, Guiloff RJ. Hypothesis on the pathogenesis of vacuolar myelopathy, dementia, and peripheral neuropathy in AIDS. *J Neurol Neurosurg Psychiatry* 1998;**65**:23–8.
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BOOK REVIEWS

Amyotrophic Lateral Sclerosis: A Synthesis of Research and Clinical Practice. Edited by ANDREW EISEN and CHARLES KRIEGER. (Pp303, £45.00). Published by Cambridge University Press, Cambridge, 1998. ISBN 0 521 58103 6.

From its very first sentence, this monograph on amyotrophic lateral sclerosis is anchored in its writers' personal experience. Its contents are, they tell us, "based on 664 patients"—"all examined by one of the authors". Professor Eisen and Dr Krieger have reviewed all aspects of the condition, from molecular mechanisms to bedside care. Their approach is essentially focused on clinical issues, but the book is also a useful introduction to the basic science. They review the diagnostic process from the standpoint of the clinic room, stressing both the rarity of conditions that mimic the disease and, in view of the gravity of the diagnosis, the vital need to seek out any potentially treatable disorder. The stamp of seasoned knowledge is particularly evident when the text turns to electrophysiology. Here, readers are offered precise advice and encouraged to perform techniques—such as recording corticomotoneuronal excitatory postsynaptic potentials—themselves.

The personal approach that underpins the book sometimes leads the argument in unexpected directions. On only the third page, studies of sex hormones are discussed to explain the male predominance in young onset cases. In this and other areas "not shared- by conventional dictum-" as the authors' preface has it, references are mainly to their own papers. In the chapter on therapy, which opens with a survey of trial methodology and reviews the underlying mechanisms of potential therapeutic agents, only four pages are spent on symptomatic treatment of the patient. This brief overview touches on, but hardly does justice to such topics as respiratory support and gastrostomy feeding—two interventions of established benefit. Moreover, it makes scant mention of the need for multidisciplinary care. For a summary of these issues, readers would find Mitsumotos's *Care and Management of the Patient with ALS* much more useful.

The superspecialist may quibble over the odd detail (there is no mention of the dual pattern of inheritance of the D90A superoxide dismutase mutation, a paradox apparently unique in inherited disease) and recent

developments, such as the role of tau pathology in ALS-dementia overlap syndromes, come too late to be included. But this volume's strengths—its clarity, brevity, and breadth of vision—are to be applauded. Where else would one find tidy one paragraph descriptions of the basis of magnetic resonance spectroscopy, or the difference between an odds ratio and a relative risk? I have already lent out my copy of this handy little one volume summation and recommend it as a launchpad for readers' further investigations into ALS/MND.

MATTHEW PARTON

John Huglings Jackson–Father of English Neurology. Edited by MACDONALD CRITCHLEY and EILEEN A CRITCHLEY. (Pp224, £39.50). Published by Oxford University Press, New York, 1998. ISBN 0-19-512339-5.

This is a fascinating historical document about one of the giants of English neurology, extensively researched and written by authors whose life and experience uniquely qualify them to provide a detailed and touching account of the life of this great man. For those of us brought up in the modem era of magnetic resonance scanning, functional imaging and complicated neurophysiological techniques, it is humbling to read about the achievements of a man whose only tools were his powers of observation and obsessive and detailed recording of what he saw in his daily practice and his ability to recognise clinical patterns of disease. Eileen Critchley provides much of the detailed pedigree research which allows us to understand those people close to Huglings Jackson who influenced him in his formative years and also provide a insight into life at the time. The well known Welsh connection is examined in detail and one cannot help but be impressed by the lengths the authors have gone to provide as much accuracy as possible. This biography takes us through the initial medical training and apprenticeship at the time at the now defunct medical school at York containing only 12 students (and no women) a year with interesting excerpts of documents providing snippets of personal information; the sole remaining letter from his father is particularly touching with some standard paternal advice extolling the virtues of prudence, in particular keeping his tailoring bill down. Huglings Jackson seemed to have been set on a career in neurology from an early age stimulated by his interest in anatomy and possibly a Bell's palsy which he developed early in his life. It was therefore not surprising that he took a well trodden path to London to insert himself into society and to learn from the great neurologists of the era. His arrival coincided with the cholera epidemic of 1862 during which his services were recognised. His subsequent academic life was awesome, his publishing life extending over 46 years providing as is well known some of our fundamental understanding of the epilepsies and in particular the aphasias which are examined in detail in this book.

I very much enjoyed reading this work which provides an authorative account of one of the founding fathers of our trade and would recommend it to neurologists young and old.

NEIL ROBERTSON

Prognosis in Neurology. By JAMES M GILCHRIST. (Pp384, £55.00). Published by Butterworth Heinemann, Oxford, 1998. ISBN 0 7506 9888.

This book is an attempt to rectify the gulf that has developed between the emphasis that has been placed on diagnosis in contemporary neurology and the pastoral care that has traditionally comprised a large proportion of a neurologist's clinical practice. It is designed as an accessible guide to prognosis in neurological disorders for both senior and junior clinicians and benefits from the contributions of nearly 100 authors. The usefulness of this book relies on the basic premise that the diagnosis has been established and is accurate, it leaves no room for manoeuvre on the grey cases with which we are all so familiar.

The chapters are short and necessarily concise, attempting as it does to cover the whole range of neurological disease. For example cerebral stroke is covered in three pages and spondylosis in a little less; multiple sclerosis and CNS lyphoma are given the same exposure. As the price of this book is £55 the fundamental question when the impoverished SpR is deciding on the direction his educational funds should take is whether this book has substantially more to offer than is available in one of the more comprehensive general textbooks of neurology. On balance I think it does but its forte is clearly the more unusual diseases rather than stroke, multiple sclerosis, and dementia. The manner in which the chapters are set out with stereotyped headings of natural history, factors affecting prognosis, evaluation for prognosis, therapies affecting prognosis, short term prognosis, and long term. prognosis allow quick and easy reference and retrieval of information.

Not an essential book, but it teaches us the importance of prognostic features in neurological disease and is likely to be a useful companion to have for interviews with patients and their relatives who are understandably willing recipients of this information.

NEIL ROBERTSON

CD-ROM REVIEW, Temporal Bone Dissector. **The Interactive Otology Reference**. By NIKOLAS H BLEVINS, ROBERT K JACKLER, and CHRISTINE GRALAPP. (£187.00). Published by Mosby, St Louis, 1997. ISBN 0-8151-4850-X.

The advances of medicine in the past two decades have been very rapid and exciting and hand in hand with this has gone advances in audiovisual aids and teaching. The technology that has brought the computer into most households has been truly amazing particu-larly for those of us who lived before the birth of the computer. This has led to a revolution in information technology and inter-communication. The world now seems a very small place, the Internet and the World Wide Web has ensured that this is the case but it has also led to the instant availability of a vast sea of knowledge about all aspects of life.

There are now new horizons in audiovisual technology and these can be utilised to teach both undergraduates and postgraduates. There are some that would say that the old fashioned apprenticeship is the gold standard in surgery but this CD-ROM by Blevins, Jackler, and Gralapp is an attempt to use computer technology to teach young surgeons the anatomy of the temporal bone and temporal bone dissection techniques. It is a totally novel idea and the authors are to be congratulated for their innovative approach.

The CD-ROM is divided into three sections, Temporal Bone Dissection which is an illustration of several operative techniques. The operator has to click on the scalpel to move it and to perform various surgical manoeuvres, similarly drills can be manipulated both with cutting burrs and diamond paste burrs. By clicking on the various anatomical structures the name of the structure appears which is a useful teaching aid. The surgical sequences, however, are somewhat simplistic and rather resemble cartoons. The operator learns by making a mistake and seeing and hearing a flow of blood indicating the haemorrhage that could ensue if, for example, a cutting burr is used over the lateral venous sinus. Although this is a wonderful way to use a computer and is certainly amusing the young otologist will not find this a substitute for hard graft in the temporal bone laboratory. The second aspect of this is a series of videos of surgical technique. Unfortunately the quality of the video is not terribly good. This may be due to technical reasons rather than to lack of preparation on the author's part.

Undoubtedly, the best aspect to this interactive otology reference is the multi-planer MRI imaging and the CT scan. MRI and CT are complementary in the skull base and the authors have utilised the computer technology wonderfully in this sphere in order to meet the challenge of identifying the anatomical structures of the temporal bone in the axial, coronal and sagittal planes. An anatomical quiz has been formulated and the operator has to identify the structure by clicking on it. He has three attempts to do so and if correct then he will be awarded a mark which is cumulative, those scoring the highest marks being awarded the title of Professor, a good score which is not quite up to the professorial mark is classified as a Fellow, Senior Resident etc, down a marking scale. This makes learning fun and adds a competitive spirit which always goes down well with surgeons. The quality of the images are excellent and it is undoubtedly this aspect of Temporal Bone Dissector CD-ROM that is most useful and is a fun and painless way of learning three dimensional temporal bone anatomy.

DAVID A MOFFAT

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A M SALVAN, S CONFORT-GOUNY, P J COZZONE, J VION-DURY, B CHABROL and J MANCINI

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