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. 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 pediatric unit, the patient presented an inappropriate gelastic affect with tangential speech but without any temporospatial desorientation. 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 concentration (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 considerable 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).

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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 with a 1.5 T and a 3 T MR scanner (Siemens Magnetom SP36, 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 (180° 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 (TTE: 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 x 2 cm x 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 (MADeluc, CBS, Montpellier, France) on a Silicon Graphics Indigo station as previously described. 

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 centered 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 GIn/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, the large decrease in NAA probably reflects the severe neuronal loss usually found in SSPE. As inositol is a glial cell marker, the increase in the inositol signal can be related to active gliosis. The lack of a mass effect related to oedema suggests that the accumulation of lactate signal shows macrophagic infiltration rather than hypoxic/ischaemic damage. The increase of a lactine signal might be related either to demyelination or to inflammation. 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 MRI. 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 not 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 glial reactivity and 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.

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

B CHABROL
J MANCINI
Service de Neuroradiologie, Hôpital d’Enfants, CHU Timone, Rue St Pierre, 13006 Marseille, France

Correspondence to: Dr Jean Vion-Dury, Centre de Résonance Magnétique Biologique et Médicale (CRBBM), 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


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 postictal coma which lasted 3 days. On both occasions haematological and biochemical tests were normal. CSF and MRI, CSF examination, and EEG were normal. A few days later, he had another tonic attack of 1 minute, with a confusional state, normal nondiphasic EEG, and left hemiplegia for 8 hours followed by stupor for 2 days. The patient was therefore admitted to our hospital to normal nondiphasic EEG, dystonia, dystymoria, tremulousness, increased deep tendon reflexes, ankle clonus, nystagmus, and an enlarged thyroid were noted. During his stay in the 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 were normal. The volume of the left nucleus caudatus, MR angiography was normal. Ictal brain SPECT showed left hemispheric hypoperfusion. Biochemical examination 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 reported 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, (lanzarine (10 mg/day) was administered.

Thyroid function investigation displayed a Hashimoto’s thyroiditis, as serum TSH concentration was 4.8 mIU/l (normal range 0.3–3.1 mIU/l), antithyroglobulin antibodies 1/1000 (normal range <100), and antithyroid antibodies TSH receptor antibodies 1/25.600 (normal range <1/100), and TSH receptor antibodies were absent. Serum T3, free T3, T4, and free T4 concentrations were normal. Fluorazil treatment was maintained for 28 months after 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 fluorazil 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 transient responsiv e 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. 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. However, Hashimoto’s encephalopathy and AHC were never reported in patients with Hashimoto’s encephalopathy, however, to our knowledge clear cut transient, recurrent, and alternating hemiplegia episodes reported 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 internal 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. 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, and left temporal hypoperfusion in another patient. Therefore, as proposed by Forchetti et al. 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. 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 Scorte, 53100 Siena, Italy. Telephone 0039 577 586522; fax 0039 577 586143; email balestri@uni.s.it

Letters, Correspondence, Book reviews

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 inset 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 inset 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 rhythmic activity of 6–7 Hz.

The effect of STN stimulation. 

Vocal dyskinesias could be related directly to the improvement of levodopa induced dyskinesias in our patient. The improvement of levodopa induced dyskinesias was observed after surgery, the motor score of the 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) in the on condition was 15. The patient was operated on bilaterally in the STN according to the method of Limousin et al. 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 and improves all parkinsonian symptoms, including levodopa induced dyskinesias, in patients with Parkinson’s disease. Although the improvement of levodopa induced dyskinesias has been attributed by Krack et al. 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 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

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-FARÍEA
Hospital “Príncipe de Asturias”, Universidad de Alcalá de Henares, Madrid, Spain

CARLOS MAGARINOS
Unit of Neuropyschology

MIGUEL ÁNGEL 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 00/34 91 4376078; fax 0034 91 3280704; email FJimenez@meditex.es


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. 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 urticaaria 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 quadrantoponia was demonstrated. Brain CT showed a left occipital infarct (figure).

She subsequently made a full recovery from the quadrantanopia. 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. In one case, 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 patients died after bee or wasp sting. At postmortem cerebral infarction was found in both. The mechanism of cerebral infarction was not alluded to.

Acute myocardial infarction has been reported four times. 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. 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, leukotrienes, and thromboxane. The venom also contains allergenic proteins such as phospholipases which elicit an IgE response, resulting in mast cell activation. Mast cell activation results in release of preformed substances such as histamine as well as de novo synthesis of other vasoconstrictors. The adrenaline that the patient was given may also have been implicated in vasoconstriction, resulting in a hypotensive state. Many of the mediators released, including thromboxane and leukotrienes, 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, optic neuritis, limb numbness, and trigeminal neuralgia and three cases of encephalopathy, one of which was fatal. Postulated mechanisms include both a toxic effect of venom and hypersensitivity to venom.

FRANCESCA CRAWLEY
FRED SCHON
Department of Neurology, Addenbrooke's Hospital, Cambridge, UK
MARTIN M BROWN
Division of Clinical Neuroscience, St George's Hospital Medical School, London, UK

Correspondence to: Dr Fred Schon, Consultant Neurologist, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK

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 with no 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 any symptoms or related 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 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. The whole 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 the control group.

### Cerebrospinal fluid manganese concentrations in patients with symmetric palidal 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 measurements in patients with symmetric palidal hyperintensities on T1 weighted MRI are significantly higher.

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

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Sex</th>
<th>Primary disease (parenteral Mn dose (mg/day)) (duration (days))</th>
<th>Serum Mn (μg/l)</th>
<th>Whole blood Mn (μg/l)</th>
<th>CSF Mn (μg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>M</td>
<td>Pyelonephritis (1.1/20)</td>
<td>1.7</td>
<td>1.6</td>
<td>6.7</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>Wvenience's encephalopathy (1.1/51)</td>
<td>2.1</td>
<td>4.4</td>
<td>3.8</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Child's grade B cirrhosis</td>
<td>2.2</td>
<td>2.4</td>
<td>3.0</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Parkinsonism (1/20)</td>
<td>1.2</td>
<td>1.6</td>
<td>2.1</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Child's grade B cirrhosis</td>
<td>2.3</td>
<td>4.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td>1.90 (0.45)</td>
<td>2.84 (1.37)</td>
<td>3.74 (1.76)</td>
</tr>
<tr>
<td>Control subjects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>Acute disseminated encephalomyelitis</td>
<td>1.5</td>
<td>1.7</td>
<td>0.7</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>Chorea-acanthocytosis</td>
<td>1.5</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>Multiple sclerosis</td>
<td>1.3</td>
<td>1.7</td>
<td>0.2</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>Neurosis</td>
<td>0.9</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>Guillain-Barré syndrome</td>
<td>1.9</td>
<td>2.0</td>
<td>0.4</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>Parkinsonism (1/20)</td>
<td>1.0</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>Malignant syndrome</td>
<td>0.8</td>
<td>1.4</td>
<td>0.2</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>Progressive supranaural palsy</td>
<td>0.9</td>
<td>1.1</td>
<td>0.3</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>Progressive supranaural palsy</td>
<td>1.2</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>Parkinson's disease</td>
<td>1.3</td>
<td>2.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td>1.23 (0.34)</td>
<td>1.64 (0.53)</td>
<td>0.47 (0.25)</td>
</tr>
</tbody>
</table>

Normal ranges: serum Mn 0.2-1.6 μg/l; whole blood Mn 1.3-3.1 μg/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 hemo-

The role of the nucleus intercalatus in vertical gaze holding

I was interested to read the report of Janssen et al of a patient with upbeat nystagmus who had a medial medullary infarct. By contrast with our patient,1 they had slow phases with a constant velocity, a “vestibular” type of nystagmus of central origin. As noted by Janssen et al, Hirose et al 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:

\[
\frac{dx}{dt} = -kx, \quad x = x_0 e^{-kt}
\]

The gradient k is the decay constant. A regression line may be fitted and confidence limits for k established. A more detailed analysis5 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”, second order linear differential equation.6

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. This may reflect the varying activity of other afferents to the perihypoglossal nuclei. Nevertheless, the approxi-
mate linearity of all the plots suggests 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 convert 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 show a non-zero gradient.

N A R MUNRO
Department of Neurology, King’s Healthcare Trust, Mapother House, Decaproy Park, London SE5 4AR, UK


Bronstein et al reply:

We thank Munro for his interest in the patient we reported in this Journal with a low medul-

lary lesion and upbeat nystagmus. 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 reader, a medical jour-
nal we should like to clarify that the integration alluded to is mathematical inte-
gration. 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 and Hirose et al,3 with large medullary lesions, had predominantly exponentially decaying slow phase velocity. Our patient, with a small paramedian lesion, had upbeat nystagmus with linearly decaying slow phase velocity.1 Following Munro’s suggestion we obtained velocity–position plots of single nys-
tagmic beats and found most of them to be linear (horizontal line on velocity-position

plots (figure). Only about 10%-15% of nystagmus 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 (orthophoria), stimulus sensitivity, we argue that a small nucleus intercalatus lesion presents clinically as a central vertical nystagmus. Larger lesions may damage additional neuronal circuits involved in ocular-motor integration.

A M BRONSTEIN
AJ JANSSEN
SF FARMER
National Hospital for Neurology and Neurosurgery
Queen Square, London, UK


“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.,

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.

"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). 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.

Our approach takes account of this fact.

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changes which impact patients’ daily lives, report before the end of a trial.

The problem of summing estimated disabil-
ity 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 of the AUC
statistic. If data on changes at different
levels of a rating scale are required, then strati-fi-
cation analysis according to baseline disability
should be carried out using any outcome meas-
ure including “confirmed progression”, over-
all 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 Mat-
thews et al., the AUC statistic is particularly
relevant for summarising peak data such as in
the increase and decrease of disability associ-
ated with a relapse. However, it is also
relevant and appropriate for the analysis of
the complete course of peaked, multiply,
and growth data, which characterises the dis-
ability course of relapsing-remitting multiple
sclerosis. If the functional form of the disabil-
ity 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
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
teoretically, irreversible disability progress-
ion in multiple sclerosis is best assessed by time
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 irrevers-
able events such as death or loss of mobility (!)
rather than those we typically use in relapsing
multiple sclerosis. Commonly employed disability end points, such as
EDSS change from study entry to comple-
tion, and the so-called confirmed progression at 3 or 6 months, have major flaws as already
discussed.

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 sum-
mary measure statistic (AUC) takes into
account both transient and permanent dis-
ability, 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 sclero-
sis.

CLARENCE LIU
LANE 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, Aiton
University, Birmingham B4 7ET, UK

4 IFNB Multiple Sclerosis Study Group. Interferon-β-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multi-
centre, randomised, double-blind, placebo-
logy 1995;45:1260–70.
6 The PRISMS Study Group. Randomised, double-blind placebo-controlled study of interferon-β-1b in relapsing-remitting mul-
7 Weinshenker BG, Rice GPA, Noseworthy JH, et al. The natural history of multiple sclerosis: a geographically based study. 4. Applications of planning and interpretation of clinical thera-

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

We read with extreme interest the article by
Tan and Guifol. 1 The excellent review
illustrates the current knowledge on trans-
methylation abnormalities in the pathogen-
esis of neurological complications of HIV
infection. It is most convincing in its ability
to bridge evidence of cytochrome activation, myel-
onetopathy, and peripheral neuropathy, with abnor-
malities of methylation in the nervous system.

Our group has been working for years on
the hypothesis that AIDS associated myel-
opathy and other HIV related neurological
disorders are consequent to an induced
metabolic abnormality of the transmethyla-
tion pathway. Our initial clinical studies with
methionine supplementation suggest that
signs and symptoms of myelopathy and
cognitive function improve with methionine
supplementation. 2 Although still prelimi-
nary, these data offer further argument for a
pathogenetic role of methylation in neuro-
logical complications of AIDS, and suggest
that a therapeutic approach aimed at correct-
ing 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, Guifol RJ. Hypothesis on the patho-

Amiotrophic Lateral Sclerosis: A Synthesis of Research and Clinical Practice. Edited by ANDREW EISEN and
CHARLES KRIEGER. (Pp303, £54.00). Published by Cambridge University Press,

From its very first sentence, this monograph on amiotrophic lateral sclerosis is anchored in its writers’ personal experience. Its con-
tents are, they tell us, “based on 664 patients”—“all examined by one of the authors, Professor Eisen”—“we 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 stand-
point 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 cortic-
comotoneuronal excitatory postsynaptic potentials—themselves.

The personal approach that underpins the book sometimes leads the unex-
pected directions. On 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 Mizuno and Grant’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 superox-
dismutase mutation, a paradox apparently
unique in inherited disease) and recent

BOOK REVIEWS

Letters, Correspondence, Book reviews

J Neurol Neurosurg Psychiatry: first published as 10.1136/jnnp.66.4.547 on 1 April 1999. Downloaded from http://jnnp.bmj.com/ on June 27, 2022 by guest. Protected by copyright.
Neurology.

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 modern 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 what 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 authoritative account of one of the founding fathers of our trade and would recommend it to neurologists young and old.

Neil Robertson


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 lymphoma 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 more likely to be to those people close to Huglings Jackson and if correct then he will be awarded a mark for his eccentricity.

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


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 particularly 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 audio-visual technology and these can be utilised to teach both undergraduate and postgraduate students. There are some that would say that the old fashioned apprenticeship is the gold standard in surgery but this CD-ROM by Bleivins, Jackler, and Gralapp is an attempt to use computer technology to teach 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 scalp 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 have been created and the operator learns by making a mistake and seeing and hearing a flow of blood indicating the significance of the structure. For example, a cutting bur 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 to armpster. 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