

PostScript

LETTERS

Delayed early morning turn "ON" in response to a single dose of levodopa in advanced Parkinson's disease: pharmacokinetics should be considered

The pathophysiology underlying the fluctuations in response following oral levodopa therapy is complex and includes peripheral and central factors. The short half-life of levodopa, erratic gastrointestinal absorption, and competitive transport across the blood-brain barrier have been regarded as factors responsible for the fluctuating plasma and striatal concentrations of levodopa. Indeed, failure of an oral dose to produce an effect or delay in the onset of action have been associated with problems in absorption.^{1,2}

We studied the pharmacokinetics of levodopa in 19 patients with advanced Parkinson's disease (12 men, seven women; period of evolution of illness more than 10 years) with and without a delayed response to the first drug dose in the morning (delayed early morning turn "ON"). The patients were selected according to the UK Brain Bank criteria; those who could not tolerate an assessment after 12 hours without taking their antiparkinsonian medication were excluded. All patients signed an informed consent form before being included in the study.

Medication and food were withheld after midnight the night before the study day. All patients' regular therapeutic first (morning) levodopa/carbidopa dose was between 125 mg and 250 mg. Therefore all patients received a single oral dose of levodopa/carbidopa (250/25 mg) at 9:00 am, to ensure that all had a response. A low protein breakfast was served three hours after drug administration.

Blood samples were collected every 20-30 minutes for six hours following drug administration. Plasma levodopa concentration was determined using high performance liquid chromatography (HPLC) with electrochemical detection as previously described.³ Peak plasma concentration (C_{max}), the time elapsed to reach the C_{max} , area under the curve, half-life, clearance, and slope in the absorption phase (K_{abs}) were determined using PK Solutions version 2 software (Summit, USA <http://www.summitpk.com/>). Motor performance was evaluated using a tapping test on the more affected side. In this test, patients are requested to alternately tap two points separated by a distance of 30 cm with the fingers of the hand (of the most affected side) for one minute. In the present study, total tapping—that is, the number of times the patient is able to carry out the task, was recorded every 20 minutes during the first two hours and then every 30 minutes until the completion of the test. The Unified Parkinson's Disease Rating Scale for motor examination (UPDRS-III) was applied prior to (baseline) and at the time of the "best on" after levodopa administration. Delayed early

morning turn "ON" was defined as the condition in which the effect of levodopa in the tapping test (a 50% basal score improvement; maximal levodopa effect = 100%) appeared more than 40 minutes after the administration of the drug.

For all patients, the results are given as mean (SD) and Student's *t* test ($p < 0.05$) was used to determine the significance between the differences.

The UPDRS-III and tapping tests were used to verify the occurrence of the drug effect, thus allowing patients with and without delayed early morning turn "ON" to be distinguished. In clinical practice, a standard dose of levodopa becomes effective within the first 20 minutes after drug administration. For separating the patients without and with delayed early morning turn "ON", the latter were considered as those in whom a standard levodopa dose took more than 40 minutes to become effective. These patients showed a tendency to have worse baseline and best ON scores than the patients without delayed early morning turn "ON", although this trend was not statistically significant.

As shown in fig 1, a significant difference was found between the C_{max} values of patients without delayed early morning turn "ON" (mean 3552 (SD 1208) ng/ml) and those of patients with delayed response (1146 (289) ng/ml). None of the other pharmacokinetic parameters showed statistically significant differences.

To obtain an adequate response in Parkinson's disease the appropriate oral dose of levodopa is usually determined bearing in mind that worse symptoms may be treated with higher drug dosages or more frequent doses as long as side effects do not appear. This simplistic approach does not take into account the evolution of the disease, in which not only do the symptoms become more evident but also the treatment progressively

loses its effectiveness. Indeed, patients with Parkinson's disease, whose illness has evolved over several years and evidence motor fluctuations tend to show a delayed response to the first oral levodopa dose compared with patients with non-fluctuating motor symptoms. The mechanism of this phenomenon is still poorly understood.⁴ In the present study, patients with delayed early morning turn "ON" had significantly lowered C_{max} values. Even though we are unable to give a direct explanation for the molecular events underlying this finding, it is clear from our data that the pharmacokinetics of levodopa play an important role in the occurrence of delayed early morning turn "ON".

Since all other pharmacokinetic parameters (including K_{abs}) of the patients with and without delayed response showed no differences, one might consider that the rate of absorption is basically the same in both groups. In addition, it has been found that both subcutaneous administration of apomorphine⁵ and pyloric bypass with duodenal infusion of levodopa⁶ are useful because they reduce plasmatic variability and improving clinical response in patients with delayed early morning turn "ON" by increasing functional "ON" time with less dyskinesia and fluctuation. Therefore, we propose that altered gastric emptying but not the intestinal absorption rate might be linked to the delay in the clinical response observed. However, further studies are necessary to address this issue.

Slower progression of the neurodegenerative process and the loss of levodopa effect are usually associated with the degeneration of dopaminergic nerve terminals in the central nervous system (pharmacodynamic factor).⁷ The data presented here highlight the need to also consider pharmacokinetic factors when analysing the delayed early

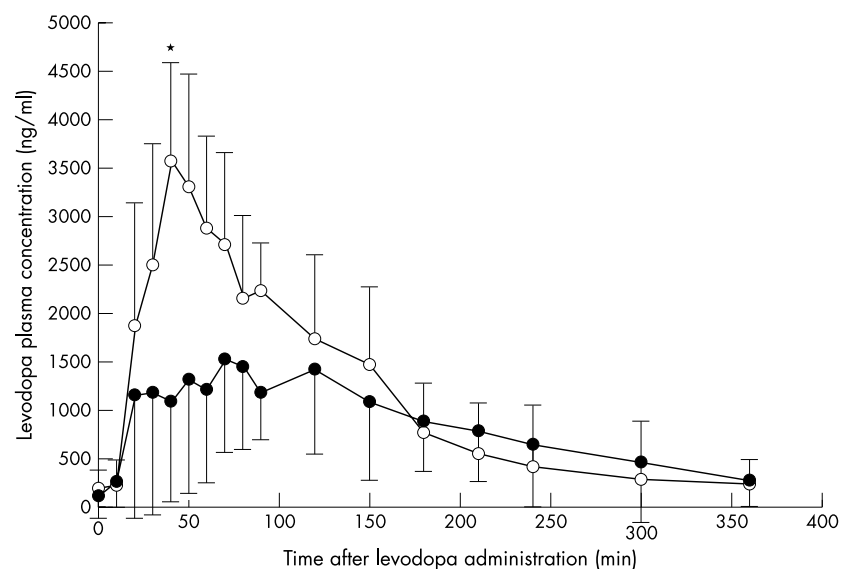


Figure 1 Pharmacokinetic curve after a single dose of levodopa. Data are shown as mean (SEM): filled circles, 12 patients with delayed early morning turn "ON"; open circles, seven patients without delayed early morning turn "ON". *, $p < 0.05$.

morning turn “ON” condition and considering the best doses and regimen of drug administration in patients with advanced Parkinson’s disease.

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P Chaná, C Kuntsmann

Movement Disorders Unit, Service of Neurology and Neurosurgery, DIPRECA Hospital, Universidad de Santiago de Chile, Chile

M Reyes-Parada, P Sáez-Briones

Neurosciences Unit, Facultad de Ciencias Médicas, Universidad de Santiago de Chile, Chile

Correspondence to: Dr P Chaná, Universidad de Santiago de Chile, Belisario Prats 1597B, Santiago, Chile; pedrochana@mi.cl

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Lethal encephalopathy in a patient with isolated nervous system vasculitis

Vasculitic neuropathy can occur in patients with connective tissue diseases. On the other hand, non-systemic vasculitic neuropathy has been established as an independent clinical entity, and the risks for systemic spread and death are small.¹ In patients with this disorder, vasculitis is limited to the peripheral nervous system (PNS), and histological evaluation is essential for the definitive diagnosis. We encountered a patient with isolated nervous system vasculitis who developed lethal encephalopathy. He had a persistently high titre of anti-GM1 IgG antibody, which is occasionally detected in patients with chronic inflammatory demyelinating polyneuropathy (CIDP).

Case report

A 67 year old man had been under treatment for type 2 diabetes for 10 years. In September 1998, he was referred to our hospital because of weight loss and numbness of the lower limbs. He was mentally alert and had exophthalmos. Muscle weakness was prominent in the distal muscles of all four limbs. Sensation was disturbed with a “stocking and glove” distribution. Deep tendon reflexes were diminished in all four extremities.

Results of laboratory examination indicated diabetes mellitus and hyperthyroidism (haemoglobin A_{1c} 6.8% (normal range 4.3–5.8); thyroid stimulating hormone <0.03 µIU/ml (normal range 0.2–3.2); free triiodothyronine 13.2 pg/ml (normal range 2.9–6.0); free thyroxine 7.65 ng/dl (normal range 0.78–2.10); antithyroglobulin antibody 3200 (normal <100); antithyroid microsomal antibody 26 800 (normal <100); antithyrotropin receptor antibody 16.1% (normal

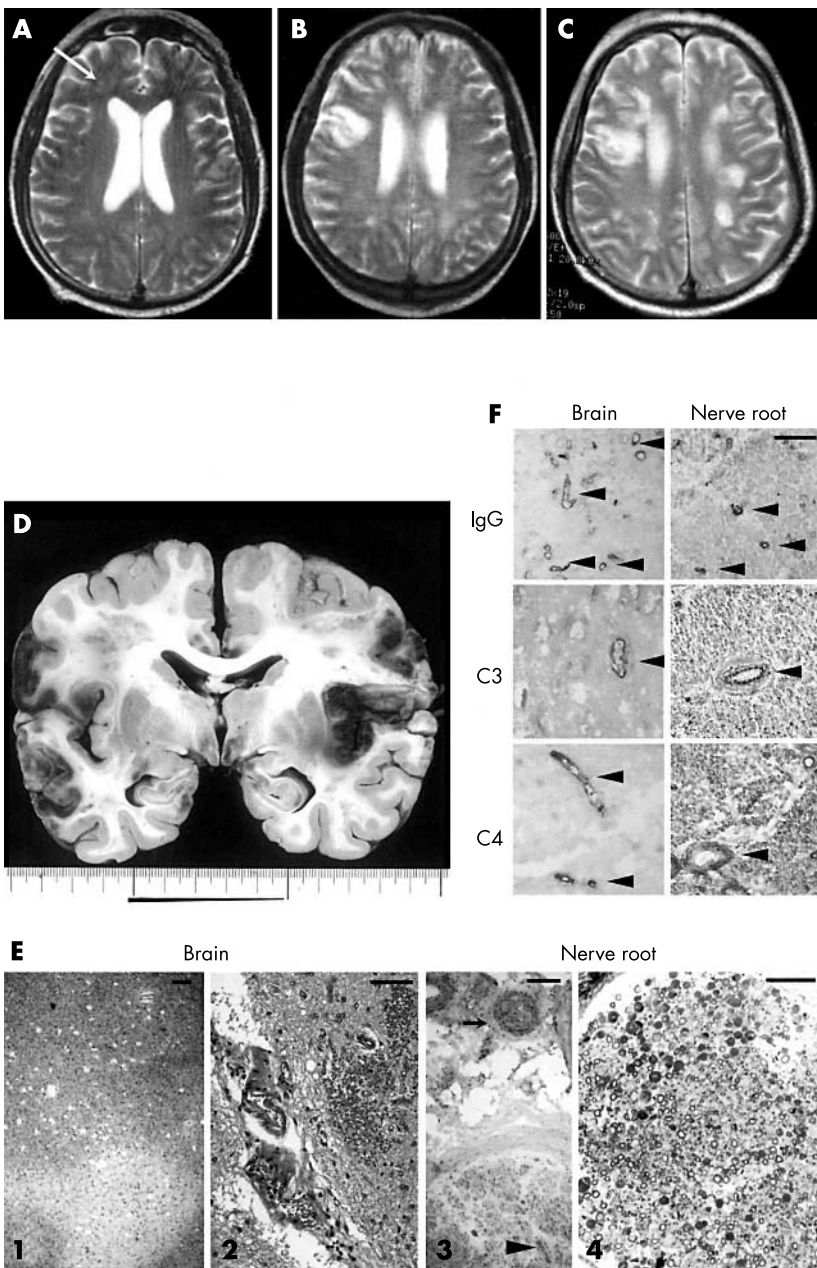


Figure 1 (A–C) Brain MRI T2-weighted images. (A) On 11 May 2000 small high intensity signals in frontal white matter (arrow) were seen. (B) On 1 June 2000, a high intensity signal appeared in the right temporal cortex. (C) On 12 July 2000, the high intensity areas were increased in number and enlarged in the cerebral cortex and white matter. (D) Coronal section of autopsied brain showed multiple plaques in white matter and multiple haemorrhagic transformations in the cortex. (E) 1—Demyelination and axonal loss in cerebral white matter (Klüver-Barrera stain); 2—haemorrhagic transformation in the temporal cortex (H&E stain); 3—vasculitic occlusion of small epineurial (arrow) and endoneurial vessel (arrowhead) in a peripheral nerve root (H&E stain); and 4—demyelination and axonal degeneration in a peripheral nerve root (toluidine blue stain). (F) Immunohistochemical staining for IgG, C3, and C4 in the temporal cortex and in a peripheral nerve root showed intense signals in the lumens of vessels. Bar, 100 µm.

<10); thyroid stimulating antibody 207% (normal <150)). Serological examination for antiganglioside antibodies revealed anti-GM1 IgG, and the titre was 25 900 (normal <800) by enzyme linked immunosorbent assay. No other antiganglioside antibodies were detected by thin layer chromatography immunoblotting. Antimyelin associated glycoprotein and antinuclear antibody were not detected. Cerebrospinal fluid (CSF) cell count was 4/mm³ and protein level was 53 mg/dl (normal <45). Oligoclonal bands and myelin basic protein were not detected.

Motor nerve conduction velocities (MCV, m/sec) and distal compound muscle action potential amplitudes (CMAP, mV) were as follows: median nerve 52.5 (normal >49) and 0.4 (normal >5); ulnar nerve 45.5 (normal >48) and 2.7 (normal >4); tibial nerve 40.0 (normal >50) and 3.8 (normal >7); peroneal nerve 36.9 (normal >48) and 1.2 (normal >3), respectively. Conduction blocks were observed bilaterally in the ulnar and peroneal nerves at the common sites of entrapment. Sensory nerve conduction velocity was 37.8 m/sec (normal >48) in the median nerve and was not evoked in the sural nerve. The patient was diagnosed as having CIDP and Graves' disease. After treatment with thiamazole, thyroid function and levels of thyroid related autoantibodies normalised but the peripheral neuropathy remained. Muscle weakness and numbness improved following treatment with prednisolone at 50 mg/day and pulse intravenous methyl prednisolone 1 g/day for three days in June 1999 but his symptoms exacerbated again after five months. Diabetes and hyperthyroidism were well controlled, but anti-GM1 IgG titre was elevated to between 11 900 and 40 700. Despite intravenous immunoglobulin (IVIg) therapy, he suddenly had convulsions and consciousness disturbance on 11 May 2000. CSF examination showed a normal cell count, but the protein level was increased to 121 mg/dl. Nerve conduction studies revealed further reduction in CMAP amplitude with conduction block and delayed MCVs. Brain magnetic resonance imaging (MRI) demonstrated slightly high intensity signals in frontal white matter on T2-weighted image (fig 1A, arrow). Intra-arterial angiography showed no evidence of a cerebrovascular accident. His consciousness disturbance responded partially to treatment with pulse methyl prednisolone, IVIg, and plasma exchange. However, a T2-weighted MRI in June 2000 showed large high intensity signals in the right frontal cortex and white matter (fig 1B). Some of the lesions were enhanced with Gd-DTPA on a T1-weighted image. In July 2000, the lesions were enlarged in the cerebral cortex and white matter (fig 1C). Despite repeated immunomodulating therapies, he died on 17 August 2000. An autopsy of the brain showed disseminated multiple plaques in the pons and bilaterally in the cerebral white matter (fig 1D), corresponding to demyelination and axonal loss (fig 1E(1)). Haemorrhagic transformations with mild infiltration of inflammatory cells in the vascular and perivascular regions were observed in the temporal cortex (fig 1E(2)) and cerebellar hemisphere. Peripheral nerve roots obtained from the lumbar plexus exhibited vasculitic occlusion of small epineurial and endoneurial vessels with inflammatory cell infiltration (fig 1E(3)) and demyelination and axonal degeneration (fig 1E(4)). Immunohistochemical study revealed intense signals for IgG, C3, and C4

in vessels from the temporal cortex, white matter, and peripheral nerve root (fig 1F), but the signals were unremarkable in specimens of unaffected regions. Vasculitis was not evident except for in the nervous system.

Discussion

The present patient showed chronic sensorimotor polyneuropathy similar to CIDP. However, the most prominent feature was lethal encephalopathy and isolated vasculitis in the nervous system. The brain lesions mainly consisted of demyelinating changes in the white matter, but the lesions in the temporal cortex and peripheral nerve roots indicated vasculitis. Immune deposits of IgG and complements were detected in the vascular regions only in the affected regions of the nervous system. The immune deposits may be associated with vascular damage resulting in cortical haemorrhagic transformation. To the best of our knowledge, this is the first report of histopathological analysis of CNS involvement in vasculitic neuropathy with no evidence of systemic collagen disease.

Anti-GM1 antibody is occasionally detected in patients with CIDP or systemic collagen disease with neurological manifestations.² However, it has not been studied in patients with non-systemic vasculitic neuropathy. Brain endothelial cells and endoneurial cells share GM1 ganglioside antigens with peripheral nerve tissues, and anti-GM1 antibody facilitates leakage in the blood-nerve barrier.³ These findings indicate that anti-GM1 antibody might have induced demyelinating change and vascular damage in both the PNS and CNS of the present patient. It is noteworthy that CNS white matter lesions have been detected in patients with CIDP.⁴ Interestingly, anti-asialo-GM1 antibody has been frequently detected in patients with Graves' disease or Hashimoto's thyroiditis.⁵ Although Graves' disease may have contributed to the development of the encephalopathy, lethal encephalopathy is an extremely unusual outcome not only in non-systemic vasculitic neuropathy but also in thyrotoxic autoimmune encephalopathy.⁶

In conclusion, vasculitic neuropathy seemed to have resulted in the development of lethal encephalopathy in the present patient. Furthermore, a common autoimmune mechanism mediated by anti-GM1 antibody similar to that in CIDP may have been involved in the lesions in the CNS as well as PNS.

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Y Sumitomo, M Kunishige

Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, Tokushima, Japan

N Satake

Department of Molecular and Environmental Pathology, University of Tokushima Graduate School of Medicine, Tokushima, Japan

K Shinno

Department of Neurosurgery, University of Tokushima Graduate School of Medicine, Tokushima, Japan

M Kawashima, T Matsumoto, T Mitsui

Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, Tokushima, Japan

Correspondence to: Dr M Kunishige, Department of Medicine and Bioregulatory Sciences, University of Tokushima Graduate School of Medicine, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan; kuni@clin.med.tokushima-u.ac.jp

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Acute combined central and peripheral inflammatory demyelination

Generally, inflammatory demyelinating diseases selectively affect either the central or peripheral myelin. Here we report a case of a severe combined central and peripheral demyelination, each of which contributed equally to the clinical syndrome.

Case report

A 32 year old female was admitted to a general district hospital with a 3 day history of aches in the legs, fever (38 °C), urinary retention and leg weakness. Neurological examination revealed a flaccid tetraparesis with abolished abdominal and ankle reflexes, diminished knee reflexes, bilateral extensor plantar responses, and sensory level at T12. The patient was given high dose intravenous prednisone (1 g) for 5 consecutive days. She became bedridden with complete paraplegia of the legs and was referred to our department. Upon admission, in addition to a flaccid tetraparesis (strength 1/5 in the legs and 4/5 to 4 ± 5 in the arms, MRC grade) with abolished abdominal, knee and ankle reflexes, extensor plantar responses, and sensory level at T5, a bilateral gaze evoked nystagmus was detected. Urodynamic examination revealed an atonic bladder. Lumbar puncture revealed a pleocytosis (34/mm³; 84% lymphocytes) and a cerebrospinal fluid (CSF) protein of 132 mg/dl. Neither intrathecal immunoglobulin synthesis nor oligoclonal bands were detected. Complete microbiological and virological investigations on CSF and blood specimens were negative. Further negative findings included serum angiotensin converting enzyme, anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and

onconeuronal antibodies. Serological testing for anti-ganglioside antibodies (Ganglio-combi test; Bühlmann Laboratories) showed elevated titres for asialo-GM1 (4283 Bühlmann titre units (BTU); normal<1700), GM1 (2855 BTU; normal<1700) and GQ1b (4117 BTU; normal<1700). Magnetic resonance imaging (MRI) of the spinal cord depicted an extensive cervicothoracic myelopathy (fig 1A–D). On MR images of the brain, multiple dot-like cortical and subcortical lesions were delineated, predominantly located in the frontoparietal gray and white matter (fig 1E–G). Electrodiagnostic studies indicated a severe symmetrical demyelinating neuropathy with reduced motor conduction velocities (right peroneal nerve 12.8 m/s, right tibial nerve 16.0 m/s, and right median 44 m/s), prolonged distal latencies (right peroneal nerve 17.1 ms, right tibial nerve 14.5 ms, and right median 5.3 ms), and prolonged or absent F waves, with MUAP displaying temporal dispersion and diminished amplitudes, and with electromyographic signs of acute denervation. The sensory action potentials and conduction velocities were normal.

A whole body computed tomography scan, a salivary gland scintigraphy scan, and a lip biopsy were completely unremarkable. A diagnosis of a combination of acute disseminated encephalomyelopathy (ADEM) and demyelinating polyradiculoneuritis was made. The patient was given 30 g of intravenous immunoglobulin for 5 consecutive days (total 150 g). By day 10 after the start of the immunoglobulin treatment, the patient could stand upright for several seconds with support. As there was no further improvement during the following 2 weeks, the therapy was increased and the patient was treated with a total of six plasma exchanges on alternate days. Five days after the final plasma exchange, the patient could make her first steps with a walker. Six weeks after the final plasma exchange, MRI of the brain and spinal cord showed dramatic regression of the T2 hyperintensities. On follow-up 1 month later, the patient could walk 250 metres with a walker. On examination, no gaze evoked nystagmus was detected. Arm strength was normal. Internal rotation of the hips, hip and knee flexors, and knee extensors were 4/5 on the right and 5/5 on the left; ankle flexors and

extensors and toe dorsiflexors were 4/5 bilaterally. The knee reflexes were sluggish and the ankle reflexes absent. Six months later the patient was able to walk 1000 metres without walking aids. The neurological examination revealed brisk knee and ankle reflexes. The 1 year follow-up showed a patient with normal leg strength and mild ataxia on heel to toe gait. The electrophysiological studies showed improvement of motor conduction velocities (right peroneal nerve 24.1 m/s, right tibial nerve 33.1 m/s, and right median 46.6 m/s) and distal latencies (right peroneal nerve 10.4 ms, right tibial nerve 9.5 ms, and right median 3.4 ms).

Discussion

Our patient presented an acute demyelinating disorder affecting the central and peripheral nervous system simultaneously. After exclusion of other causes, the central nervous system involvement resembled the clinical and radiological characteristics of ADEM with long segmental spinal cord lesion. The peripheral nervous system involvement displayed the clinical, electrodiagnostic, CSF,

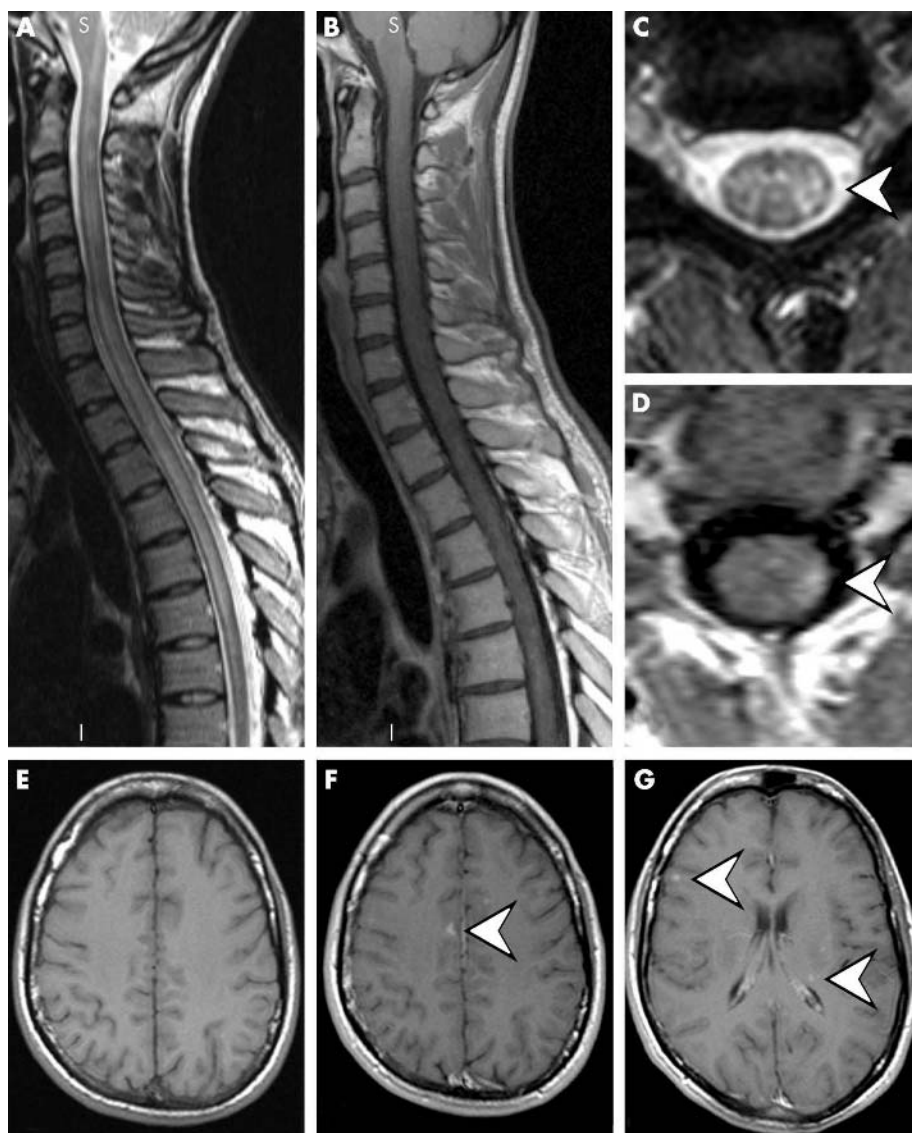


Figure 1 T2 (A, C) and T1 (B, D) weighted, contrast enhanced MR studies of the cervicothoracic spine. Confluent hyperintensities covering all imaged spinal segments are depicted (A), some of which show patchy enhancement (arrows) subsequent to gadolinium administration, predominantly affecting the spinal column dorsolaterally. T1 weighted MR images pre (E) and post (F, G) contrast. Small dot-like cortical and subcortical lesions are seen, showing contrast enhancement (arrows).

and serological features of a demyelinating polyradiculoneuropathy.

Documented overlap of acquired acute central and peripheral system demyelination is very rare. Gamstrop and Blennow used the descriptive diagnosis of encephalomyelorradiculoneuropathy to designate paediatric cases of Guillain-Barré syndrome with presumed CNS involvement.¹ Again in children, Amit *et al.* coined the entity of acute severe combined demyelination for cases in which central and peripheral nervous system pathology equally contributed to the overall clinical picture.² An acute or subacute combined central and peripheral myelinopathy has been very rarely reported in adults,^{3,4} with no successful treatment regimens being documented.

In our patient, no improvement was seen after high dose intravenous prednisone therapy (5 g), but she dramatically improved on intravenous immunoglobulin and plasma exchange therapy. This finding extends the previous reports of the effectiveness of this therapeutic strategy in the patients with central or peripheral inflammatory demyelination who failed to respond to high dose steroid therapy. Even a delayed treatment (7 weeks after onset of the symptoms) with immunoglobulin induced a significant remission. Further clinical improvement was achieved with subsequent plasma exchange. Our finding supports the concept of immunomodulation using immunoglobulin and plasma exchange in steroid resistant combined central and peripheral inflammatory myelinopathy.

Acute demyelinating diseases are often preceded by an infection or vaccination and considered to be immune mediated. This case of a severe unrestricted demyelinating syndrome encourages the concept that an immunological attack can be directed against central and peripheral myelin in susceptible individuals.

J Katchanov, J D Lünemann, F Masuhr, D Becker, M Ahmadi, J Bösel, R Zschenderlein

Departments of Neurology, University Hospital Charité, Humboldt-University, Schumannstr. 20/21, 10117 Berlin, Germany

S Bamborschke

Department of Neurology, Brandenburg-Klinik, Brandenburgallee 1, 16321 Bernau-Waldsiedlung, Germany

R Klingebiel

Department of Radiology, Neuroradiology Section, University Hospital Charité, Humboldt-University, Schumannstr. 20/21, 10117 Berlin, Germany

Correspondence to: Dr J Katchanov, Klinik fuer Neurologie, Campus Charité Mitte, Schumannstr. 20/21, D-10117 Berlin; juri.katchanov@charite.de

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Miller Fisher syndrome associated with *Pasteurella multocida* infection

Miller Fisher syndrome is characterised by ataxia, areflexia, and ophthalmoplegia and was first described by Charles Miller Fisher in 1956 as an unusual variant of acute idiopathic polyneuritis. There is frequently an antecedent illness¹ and the syndrome is associated with a high titre of anti-GQ1b antibodies in approximately 90% of cases.^{1,2} *Pasteurella multocida* is a Gram negative bacteria, commonly found in the saliva of animals, particularly cats.³

We present the case of a 70 year old lady who developed Miller Fisher syndrome with positive anti-GQ1b antibodies 11 days after *P. multocida* was cultured from a blood sample. Miller Fisher syndrome associated with *P. multocida* infection has not, to our knowledge, been described previously.

Case report

A 70 year old lady presented with a one day history of a painful left hip, fever, sweats, and lethargy following a bite from her pet cat on her left leg on the preceding day. She reported no other recent illnesses. She had had a total left hip replacement four years previously. On examination she was hypotensive and pyrexial with local tenderness of her left hip and decreased range of movement. She had puncture marks on her left shin from the cat bite with surrounding erythema tracking proximally to the groin. Initial blood cultures revealed heavy growth of *P. multocida* sensitive to penicillin. Intravenous benzylpenicillin (1.2 g four times daily) was administered.

The patient's pyrexial illness improved over the next 11 days but then she developed diplopia. The attending orthopaedic surgeon recorded that the cranial nerve examination was normal. By the following day the patient had also become ataxic, and she was referred for a neurological opinion. Examination at this stage revealed marked truncal ataxia and complete internal and external ophthalmoplegia with bilateral ptosis. Limb examination revealed areflexia and ataxia although limb power and sensation were normal. The patient was unable to stand.

A computed tomography brain scan was normal. Magnetic resonance imaging was precluded by claustrophobia. The cerebrospinal fluid was clear, containing 0.5 g/l protein, 3.3 mmol/l glucose, no white cells/mm³, and 255 red cells/mm³. No organisms were seen or cultured. There was no clinical response to pyridostigmine and acetylcholine receptor antibodies were negative. A sample of blood taken seven days after the onset of neurological symptoms was positive for anti-GQ1b antibodies at a titre of 1:1600 using enzyme-linked immunosorbent assay (ELISA). The testing laboratory considered a titre above 1:100 to be positive for anti-GQ1b antibodies. Other antiganglioside antibodies and follow up anti-GQ1b antibodies were not tested.

A diagnosis of Miller Fisher syndrome was made and intravenous immunoglobulin

(0.4 g/kg daily for five days) was administered with gradual improvement in symptoms and signs over the next six weeks leading to the patient's discharge. At follow up five months later she had fully recovered.

Discussion

This patient developed the typical neurological symptoms of Miller Fisher syndrome with positive anti-GQ1b antibodies 11 days after *P. multocida* was cultured from a blood sample. To our knowledge this is the first reported case of any form of Guillain-Barré syndrome associated with *P. multocida* infection.

P. multocida is a small Gram negative coccobacillus⁴ and is an important animal and human opportunistic pathogen. In humans it can cause soft tissue, respiratory, urinary tract, and meningeal infections. The mechanisms by which *P. multocida* might cause Miller Fisher syndrome (we are assuming causation and accept we have only demonstrated temporal association) are unknown but molecular mimicry is a possibility. There is considerable evidence supporting the theory of molecular mimicry between lipopolysaccharide (LPS) from *Campylobacter jejuni* and the GQ1b ganglioside.⁵ As *P. multocida* is Gram negative, its capsule similarly has LPS. However, we were unable to find any research specifically suggesting a similarity between the *P. multocida* LPS and the GQ1b ganglioside. *P. multocida* has previously been reported in association with acute disseminated encephalomyelitis⁴ but not, to our knowledge, with any other diseases with a presumed autoimmune basis.

Although an antecedent illness has frequently been noted before the onset of Miller Fisher syndrome the causative agents are not as well described as in Guillain-Barré syndrome.⁵ While *C. jejuni* has been implicated in the pathogenesis of Miller Fisher syndrome following enteritis, a recent study¹ of 50 patients with the syndrome found that 76% had respiratory symptoms in the month preceding onset of the syndrome compared with only 4% with gastrointestinal symptoms. *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, *Coxiella burnetii*, cytomegalovirus, Epstein-Barr virus, varicella zoster, and mumps virus have also been reported as antecedent agents in Miller Fisher syndrome. However, a statistical correlation with Miller Fisher syndrome has only been shown for *M. pneumoniae*⁵—serological evidence of recent infection was found in 7% of Miller Fisher patients compared with 2% of patients with Guillain-Barré syndrome.

From the above discussion it is clear that the antecedent illness in Miller Fisher syndrome commonly takes the form of a respiratory infection of unknown aetiology. *P. multocida* can cause respiratory infection. It is often difficult to isolate this organism from sputum samples³ and it has been reported as causing indolent and asymptomatic pulmonary infection,³ including asymptomatic lung abscess. For these reasons *P. multocida* infection is possibly underdiagnosed. Therefore, while we believe this is the first reported case of an association between Miller Fisher syndrome and *P. multocida* we believe it highly unlikely to be unique.

L P Bennetto

Institute of Clinical Neurosciences, University of Bristol, Glial Cell Research Laboratory, Frenchay Hospital, Bristol, UK

P Lyons

Department of Neurology, Royal United Hospital, Bath, UK

Correspondence to: L P Bennetto; luke.bennetto@bris.ac.uk

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Coagulopathy and NICE recommendations for patients with mild head injury

Management of patients with mild head injury (MHI) is open to debate.¹ In the last few years, there has been a trend towards earlier diagnosis, implying an extensive use of computed tomography (CT), rather than admission and observation. The National Institute for Clinical Excellence (NICE) has recently proposed new evidence based recommendations on all steps of the management of patients with MHI.² In the diagnostic algorithm, coagulopathy (history of bleeding, clotting disorder, or current treatment with warfarin) is not considered a predictor variable necessitating early CT in subjects without loss of consciousness (LOC) or amnesia since injury. This statement conflicts with previous guidelines, where history of coagulopathy, independently of symptoms, indicated CT.³

Since 1999, all cases with MHI attending the Emergency Department of our district hospital have been treated and registered in a comprehensive database according to predefined procedures.³ Our criteria for CT and/or hospital admission are wider than the NICE criteria; in particular, there is routine detailing of NICE variables, but in addition, all subjects with coagulopathy have an early CT, independently of symptoms and signs after injury. This provides the opportunity to determine the risk related to coagulopathy and the accuracy of the NICE recommendations.

We analysed the data of 7955 consecutive patients within 24 hours from trauma, who had been triaged for an acute MHI. MHI was defined as an injury of the head, other than any superficial injury to the face, Glasgow Coma Score (GCS) definitely 14 or 15, in subjects aged ≥10 years. We excluded 1258 more patients because of unclear history of the trauma as primary event, major trauma with unstable vital signs, GCS <14, penetrating injuries, pregnancy, or voluntary discharge. All patients re-attending for complaints after discharge (282 cases) underwent a CT scan and in this study were considered only once. All patients received

written recommendations at discharge for home observation and complaints that would require referral back to hospital for further evaluation. Observers were instructed to check for symptoms and signs, and for any change in patients' clinical status for 7 days.

According to NICE, CT scan is recommended in the presence of: (a) GCS <13 at any point and/or equal to 13 or 14 at 2 hours after injury, (b) any sign of basal skull fracture, (c) any focal neurological deficit, (d) post-traumatic seizure, (e) vomiting (>one episode), and (f) amnesia of events before impact >30 minutes, (g) risk factors (coagulopathy, age ≥65 years, dangerous mechanism of injury), provided that patients have experienced some LOC or amnesia since injury. In our protocol,⁴ CT is mandatory for subjects with risk factors, in particular amnesia and/or LOC (but excluding old age), independently of signs and symptoms.

Following our protocol, 4081 out of 4547 (89.8%) eligible patients had an early CT scan. In 3580 early CT was also indicated according to the NICE protocol; in 501, CT scans were performed in subjects outside the NICE protocol. These patients had CT because of coagulopathy (warfarin therapy) in 66 cases (13.2%), diffuse headache in 178 cases (35.5%), previous neurosurgical intervention in 26 cases (5.2%), history of seizures in 22 cases (4.4%), dangerous mechanism of injury in 172 cases (34.3%), and recent alcohol and/or drug misuse in 58 cases (11.6%).

Clinically important intracranial lesions were demonstrated in 477/3580 (13.3%) patients of the NICE group. Neurosurgical intervention was required within 7 days in 97 patients (2.7%) for haematoma evacuation or for elevation of depressed skull fracture. At follow up (6 months), 36 patients (0.1%) had an unfavourable outcome (death, persisting vegetative state, or severe disability by the Glasgow Outcome Scale), rated by an expert physician on the basis of a structured telephone call.

In the 501 NICE negative cases, 40 patients (8.0%) had an intracranial haemorrhagic lesion: intracerebral haematoma (20 cases); intracerebral haematoma plus subarachnoid haemorrhage (2); intracerebral haematoma plus subdural haematoma (3); subarachnoid haemorrhage (2); subarachnoid haemorrhage plus subdural haematoma (1), subdural

haematoma (11); and epidural haematoma (1). This prevalence is lower compared with NICE positive cases (Fisher's exact test, p = 0.0006), but nevertheless NICE recommendations would not have led to early detection of these 40 lesions, for which neurosurgical intervention was required in five (12.5%): intracerebral haematoma evacuation (1 case), subdural haematoma (3), subarachnoid haemorrhage plus subdural haematoma (1). At follow up, only one patient died after 9 days for causes related to intracerebral haematoma, the remaining having a favourable outcome. In these 40 NICE negative cases with haemorrhagic lesions, coagulopathy was the main factor leading to CT scan in 16 cases (40%), and was associated with a fivefold increase in the risk of intracranial lesions (table 1). With logistic analysis, coagulopathy was the only predictor variable associated with CT lesions in asymptomatic patients not fulfilling NICE criteria for early CT. Six patients, re-evaluated for complaints after a median (interquartile range) time of 144 hours (66 to 168), had an intracranial lesion detected by a second CT; four belonged to the NICE positive group, two were in the NICE negative. None had coagulopathy.

The post hoc analysis of our prospective database demonstrates that NICE recommendations for CT scanning identify the majority of patients with intracranial lesions in subjects attending the ED for MHI. However, the exclusion of coagulopathy as a factor always indicating CT impairs the diagnostic accuracy of NICE guidance. Routine use of CT scanning is not cost effective; more than 90% of CT scanning are negative in subjects with MHI, and at least 98% are negative for epidural haematoma, the event requiring immediate intervention. A more liberal policy for CT use, making CT mandatory in patients with coagulopathy, independently of head trauma severity, would indicate only 66 additional CT in our total cohort of 3581 (less than 2.0%), with a 1:4 probability of identifying an intracranial lesion.

The indications for CT use in MHI are subject to a continuous debate.³ Our data strongly suggest that the restrictive use of CT proposed by NICE in the presence of risk

Table 1 Characteristics of the 501 patients, submitted to early CT scan according to protocol, and not considered by NICE recommendations

	CT negative (n = 461)	CT positive (n = 40)	Odds ratio (95% CI)	P value*
Median (IQR) age, years	53 (29 to 77)	68 (46 to 78)	-	0.054
Median (IQR) INR†	2.3 (2.0 to 2.8)	2.2 (2.2 to 2.6)	-	0.464
Cause of injury				
Fall	204 (44.3%)	19 (47.5%)	1.14 (0.59 to 2.18)	0.741
Crash	179 (38.8%)	15 (37.5%)	0.94 (0.48 to 1.84)	1.000
Assault	15 (3.3%)	2 (5.0%)	1.56 (0.34 to 7.10)	0.637
Occupational	32 (6.9%)	2 (5.0%)	0.71 (0.16 to 3.06)	1.000
Risk factors				
Coagulopathy	50 (10.8%)	16 (40.0%)	5.48 (2.73 to 11.00)	<0.001
Dangerous mechanism	156 (33.8%)	16 (40.0%)	1.30 (0.67 to 2.53)	0.488
Age ≥65 years	191 (41.4%)	22 (55.0%)	1.73 (0.90 to 3.31)	0.133
History of epilepsy	20 (4.3%)	2 (5.0%)	1.16 (0.26 to 5.15)	0.692
Previous neurosurgery	26 (5.6%)	1 (2.5%)	0.43 (0.06 to 3.25)	0.713
Alcohol and/or drugs	51 (11.1%)	7 (17.5%)	1.71 (0.72 to 4.05)	0.205

CI, confidence interval; *Mann-Whitney U test or Fisher's exact test: p<0.05; †international normalised ratio in patients with coagulopathy.

factors may be generally accepted. However, in the light of our data we suggest that CT should also be considered for all subjects with coagulopathy.

A Fabbri, A Vandelli

Dipartimento Emergenza-Urgenza Accettazione,
Ospedale Morgagni-Pierantoni, Azienda Unità
Sanitaria Locale di Forlì, Italy

F Servadei

Unità Operativa di Neurochirurgia per la
Traumatologia, Ospedale M Bufalini, Azienda Unità
Sanitaria Locale di Cesena, Italy

G Marchesini

Alma Mater Studiorum, Università di Bologna, Italy

Correspondence to: Dr A Fabbri, Dipartimento
Emergenza-Urgenza Accettazione, Ospedale
Morgagni-Pierantoni, Azienda Unità Sanitaria Locale
di Forlì, via Forlanini 34 - I - 47100 Forlì, Italy;
andfabbri@libero.it

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Neurogenic T wave inversion in pure left insular stroke associated with hyperhomocysteinaemia

Alterations in cardiac depolarisation and repolarisation are reported in 74% of patients with cerebrovascular events.¹ They are more frequent after subarachnoid and intracerebral haemorrhage, but may also occur in acute ischaemic stroke (15–30%) and are related to an increased incidence of malignant arrhythmia and sudden death (6%).²

The most common ECG alterations are QT prolongation, ST segment alterations, T wave flattening or inversion, and abnormal U waves.¹ ECG changes may be similar to those commonly observed in patients with coronary artery disease,² but they have also been demonstrated in the absence of autopsy proven heart disease.¹ This suggests a neurogenic rather than a primary cardiac cause, mediated by unbalanced autonomic control.

Experimental evidence implicates the insular cortex in cardiovascular control and heart chronotropic organisation,² and suggests its involvement in the genesis of adverse neurogenic ECG alterations.

Case report

A 68 year old right handed female was admitted after the acute onset of mild right ataxic hemiparesis, right facial and hypoglossal nerve palsy, and dysarthria. The patient was vegetarian, had no history of diabetes or cardiac disease, and was a non-smoker without relevant family history. Blood pressure was 150/100 mm Hg and heart rate (HR) was 94 beats per minute (bpm). The admission brain CT and Doppler ultrasounds were normal. A left anterior hemiblock was detected at ECG (fig 1C).

Standard blood chemistry showed macrocytic anaemia, with other parameters within normal range, including serum lipids (lipoprotein a, total, HDL, and LDL cholesterol, and triglycerides). Antithrombin III, PT, PTT, fibrinogen, protein C and S activity, and activated protein C resistance were normal. Searches for lupus anticoagulant, antinuclear antibodies, antibodies to extractable nuclear antigens, anti-neutrophil cytoplasm auto-antibodies, anticardiolipin antibodies, and cryoglobulins were negative.

A homocysteine serum level of 35.7 $\mu\text{mol/l}$ (normal values: $<20 \mu\text{mol/l}$), vitamin B12 deficiency (90 pg/ml; normal values: 200–1000 pg/ml), and normal folic acid were detected. Vitamin B12 and antiplatelet therapy were started. The patient's clinical condition improved and 5 days later she was discharged.

The day after discharge she was readmitted because of the recurrence of moderate right ataxic hemiparesis, dysarthria, and non-fluent aphasia with phonemic paraphasia, anomia, and with essentially preserved comprehension and repetition. Blood pressure was 130/90 mm Hg and HR was 92 bpm. Blood examination showed the previously detected macrocytic anaemia, and a C reactive protein (CRP) value of 2.14 mg/dl (normal value: $<0.8 \text{ mg/dl}$). Brain CT and MRI (fig 1A and B) showed an infarct limited to

the left insular cortex with no other lesions on the diffusion weighted images.

The admission ECG showed a global T wave inversion (fig 1D), which persisted on subsequent monitoring, and disappeared only after 2 months. No other ECG alterations were detected, including QT prolongation (QT = 0.34; QTc = 0.42 s). The patient had no cardiac symptoms and transthoracic echocardiography was normal as was serum potassium, calcium, and cardiac enzyme (creatine kinase-MB, troponine I, and myoglobin) investigation repeated over 5 days.

Following 3 weeks of therapy, vitamin B12 and homocysteine levels were normal, CRP value was 1.87 mg/dl, and the macrocytic anaemia had improved.

By 2 months after the cerebrovascular events, macrocytic anaemia was absent, homocysteine, vitamin B12, and CRP were normal, and the ECG had nearly normalised. An adenosine-thallium scan performed 6 months after stroke onset showed no evidence of coronary artery disease. To date there have been no cardiac events.

Comment

Acute insular stroke may present with various clinical presentations, due to the anatomic and functional complexity of the insular lobe and its wide connections with the frontal, temporal, parietal, and olfactory cortex, and with the basal ganglia, thalamus, and limbic structures.^{3,4} It is an important gustatory, somatosensory, and visceral motor sensory processing area, a component of the vestibular and limbic cortex, and is implicated in pain processing, volitional swallowing, cardiovascular control, and cerebrogenic sudden death.^{2–4}

Pure insular strokes, rare entities in clinical practice, are defined as infarcts restricted to the insula in which coexisting brain lesions are exclusion criteria, with the exception of some involvement of the claustrum and capsula externa.⁴ This definition is justified by the complex insular arterial supply which principally supplies the insular cortex, the capsula externa, and the claustrum, and, sporadically, the capsula externa.⁴

The prominent clinical features of our case were neuropsychological disorders (expressive aphasia, dysarthria, verbal memory impairment), and electrocardiographic alterations, represented by persistent T wave inversion.

Neurogenic ECG alterations are often transient, but cause diagnostic problems, mimicking acute myocardial infarction. Some features of T waves may be suggestive of heart pathology, but they are non-specific, making it important to consider a neurogenic genesis to avoid unsuitable therapies.

The neurogenic nature of T wave inversion in our case was demonstrated by the lack of evidence of coronary artery disease or cardiac pathology, both of which were ruled out by echocardiography and adenosine-thallium scan. Myocardial enzymes, which have also been reported to be elevated mainly in large size stroke, were normal probably because of the limited extent of cerebral infarction.

In insular stroke the pathophysiology of abnormalities of rate, rhythm, and conduction is related to an imbalance of autonomic cardiovascular control and to increased circulating and local myocardial tissue catecholamines, suggesting an underlying sympathetically mediated mechanism. The insular cortex has been shown experimentally

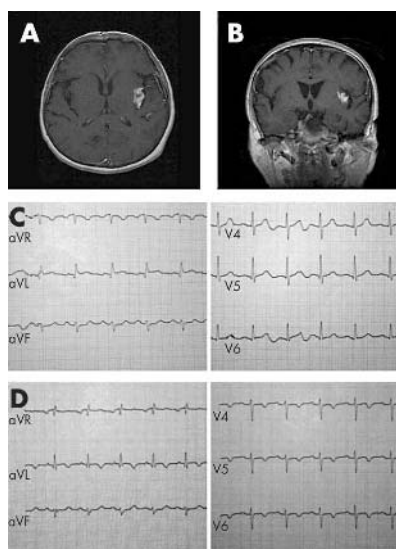


Figure 1 (A, B) T1 weighted spin echo axial and coronal scan (repetition time, TR = 500 ms; echo time, TE = 10 ms), showing the pure left insular stroke; (C) admission ECG showing only a left anterior hemiblock; (D) ECG performed 7 days after the second stroke showing the presence of neurogenic T wave inversion.

to contain an arrhythmogenic centre implicated in neurogenic electrocardiographic changes.²

There is evidence of cortical asymmetry in the regulation of cardiovascular functions: the left insula is concerned mainly with control of parasympathetic cardiac drive, and the right with control of cardiovascular sympathetic tone.^{1,2} Damage to the left insular cortex by stroke may shift sympatho-vagal balance towards increased basal sympathetic tone (a pro-arrhythmic condition), with a decrease in the randomness of HR variability, and may contribute to the excess cardiac mortality following stroke.^{1,2}

Insular infarcts so far reported are caused by artery to artery or cardiac embolisms.⁴ To our knowledge this is the first reported case of insular stroke associated with hyperhomocysteinaemia, which is an emerging independent risk factor for stroke and for vascular recurrence after ischaemic stroke.⁵

In conclusion, persistent neurogenic T wave alteration due to a left insular infarct associated with hyperhomocysteinaemia is reported in this paper. The case underlines the functional complexity of the insular cortex, its role in the generation of cardiovascular changes, and the importance of cardiac monitoring in stroke patients.

J Mandrioli, A Zini, M Cavazzuti, P Panzetti
Department of Neuroscience, University of Modena and Reggio Emilia, Modena, Italy

Correspondence to: Dr Jessica Mandrioli, Neurological Clinic, Department of Neuroscience, University of Modena and Reggio Emilia, Policlinico di Modena, Via del Pozzo n. 71, 41100 Modena, Italy; jessicamandrioli@hotmail.com

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Prion disease at a regional neuroscience centre: retrospective audit

Timely diagnosis of prion disease is vital if appropriate information and psychosocial support is to be made available to patients and families and appropriate arrangements made for symptomatic treatment and provision of palliative care. For many of these issues optimal management remains uncertain. Guidelines have been published by the Creutzfeldt–Jakob disease (CJD) Support Network¹ suggesting that a “carefully coordinated multidisciplinary team” is required to provide a “flexible, family-centred approach, with specialist CJD and palliative care services”, with appointment of a keyworker “as soon as possible” to tailor appropriate response. The optimal location of the

palliative care is acknowledged to depend on individual circumstances, but it is recognised that “acute neurology or psychiatric units cannot provide the appropriate environment for longer term care”. The guidelines explicitly do not address general palliative nursing care issues.

Most reports on cohorts of patients with prion disease have emanated from national referral centres. However, it is widely accepted that delivery of patient care close to or at home is the ideal. In many cases, this means regional neurological facilities. We undertook an audit of all pathologically confirmed prion disease cases seen in the catchment area of the Walton Centre for Neurology and Neurosurgery (WCNN), a regional neuroscience centre in Liverpool, UK, serving a population of around 3 million people and 14 district general hospitals (DGHs) in northwest England and north Wales, over a 12 year period (1990–2001) prior to publication of the CJD Support Network guidelines, to ascertain what management plans had been formulated or implemented for patients with prion disease.

Cases were identified through individual consultant neurologists and from the National Creutzfeldt–Jakob Disease Surveillance Unit (NCJDSU) in Edinburgh (Professor R G Will, personal communication). Symptomatic interventions and management of the terminal phase of the illness were ascertained by case note review, in particular, decisions about patient hydration and “do not resuscitate” (DNR) orders.

From 1990 through 2001, 82 patients with suspected CJD were referred from the Mersey Region to the NCJDSU (41 males, 41 females; average age 60.1 (SEM 19.7) years, range 14–90; eight patients ≤30 years). Of these, 65 referrals were made after 1995 when the epidemic of variant CJD (vCJD) in the UK began. A total of 66 patients (80%) presented initially to non-neurologists and 44 referrals were of inpatients at WCNN, usually transferred from DGHs by visiting neurologists. A total of 38 cases were referred to NCJDSU directly from DGHs or from Alder Hey Children’s Hospital, Liverpool.

Prion disease was confirmed pathologically in 43/82 referrals, giving an overall diagnostic accuracy of 52%. Of the cases with confirmed prion disease, 33 had sporadic CJD, 8 had vCJD (some already reported^{2,3}), and 2 had iatrogenic disease. There were no familial cases. Three patients never saw a neurologist. Of the 39 non-prion cases, eight were found to have alternative diagnoses only at post mortem, principally Alzheimer’s disease and dementia with Lewy bodies.

In none of the 43 cases with pathologically confirmed prion disease could a keyworker coordinating care be identified from case note review. Various symptomatic treatments for myoclonus, the commonest movement disorder, were tried, namely sodium valproate, clonazepam, baclofen, diazepam, and phenytoin. An empirical course of steroids to treat an undiagnosed vasculitis or autoimmune disease was given in a few cases, without benefit.

It was recorded in the notes of 32 patients (75%) that when oral fluid intake proved insufficient, fluids were given by the subcutaneous, nasogastric, or intravenous route to maintain adequate hydration. The families of only two patients opted to have a percutaneous endoscopic gastrostomy (PEG) tube placed: in one patient this continued to be in use for nearly three years, in the other, only for a period of weeks before death.

Various symptomatic treatments were used to relieve distress in the terminal phase of disease, namely diamorphine, midazolam, and cyclomorphine. In only nine cases (21%) was there any comment about cardio-respiratory resuscitation policy. In seven cases it was explicitly stated that the patient was not for resuscitation; in one case the family did not agree to a DNR policy, and in one case it was not clear what policy, if any, was agreed. All the patients died in hospital; none went to a hospice. One patient with sporadic CJD temporarily went to a nursing home, before returning to hospital to die. Nursing home placement was considered for one other patient, but the family preferred the patient to stay in hospital.

Although there are hopes for the efficacy of agents such as mepacrine and PPS, disease modifying treatment for prion disease does not currently exist. Hence, once the diagnosis is made, management is symptomatic (for example, for movement disorders, especially myoclonus, seizures, autonomic and sleep disorders, swallowing problems, and pain) and care is palliative. This being the case, provision of information and psychosocial support is of paramount importance. In the UK, patients and carers may contact various resources, such as the NCJDSU and the National Care Co-ordinator,⁴ the National Prion Clinic, the CJD Support Network, the Human BSE Foundation, and the CJD Advice Network (Department of Health). However, these agencies may not be able to provide local solutions to the care needs of patients and families affected with prion disease. Difficulties in finding appropriate locations for palliative care of patients with vCJD have been documented,⁵ leading the Department of Health to create a National Care Package.⁴

The heterogeneity of management revealed by our audit most likely reflects uncertainty about the optimal management of prion disease, and the absence of specific guidelines during the time covered by the audit. The development of guidelines and integrated care pathways which can address the specific issues facing patients with prion disease and their relatives in a comprehensive yet flexible manner may be helpful, although again disease rarity suggests that completing the audit cycle may be a long process. Coordination and support from at least one dedicated health professional in each regional neuroscience centre, to ensure implementation of guidelines¹ and to work with local agencies such as palliative care teams, currently seems an appropriate response.

Acknowledgements

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A J Larner, M Doran

Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool, UK

Correspondence to: Dr Larner, Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Lower Lane, Fazakerley, Liverpool, L9 7LJ, UK; a.larner@thewaltoncentre.nhs.uk

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BOOK REVIEWS

Myopathies in clinical practice

Edited by Phillip R J Barnes and David Hilton-Jones. Published by Martin Dunitz, London, 2003, £49.95 (hardcover), pp 161. ISBN 1-899066-71-3

Text books come in two forms; some attempt to tell you all there is to know while others try and tell you what you need to know. The editors' introduction to this book suggests that it falls into the latter category but in fact it "punches above its weight" with regard to the depth of coverage in a number of the chapters and includes observations, reminders, and pointers that all myologists, let alone general neurologists, will find extremely valuable.

Beyond the superficial level, neuromuscular disorders are complicated mainly because we now know so much about their underlying molecular biology. This book goes as far as reasonably possible in making these complexities understandable. It is divided into two sections. The first deals with basic principles, including clinical assessment and the investigation of muscle disease. The writing style is direct and almost conversational—in the style of a tutorial, which many

will find attractive. The section on investigation of muscle disease is particularly clear and comprehensive with a helpful exposition on the basics of electromyography in muscle disease and neuromuscular transmission disorders. This section concludes with a chapter on the principals of therapy of neuromuscular disease—a topic which is usually tucked away in the back of a more typical text book—perhaps reflecting the Editors very positive attitude to this aspect of this speciality. To quote them, to say that there is "nothing that I can do for you" is indeed a sad reflection on the lack of a holistic or rehabilitative approach from the clinicians involved.

The second section deals in turn with the muscular dystrophies, inflammatory myopathies, muscle channelopathies, metabolic myopathies, and the toxic and endocrine myopathies, and concludes with chapters on congenital myopathies and miscellaneous muscle disorders. The final chapter on neuromuscular junction disorders is included for the sake of completeness. Each of these chapters is to a similar high standard, although I would comment that there is no obvious logic in the way that these are ordered in the book. There is also a comprehensive index that proves efficient on several occasions.

This volume is commendably short and the text is arranged in a double column format. The production is lavish, profusely illustrated in colour with many diagrams and text boxes, which are beautifully clear. For general neurologists, I think this book will have few serious rivals as a convenient, modern, and comprehensive source of information on the most important aspects of muscle disease, and I can recommend it most highly.

R J M Lane

The central nervous system structure and function—third edition

Edited by Per Brodal. Published by Oxford University Press, Oxford, 2003, £49.50 (hardback), pp 495. ISBN 0-19-516560-8

This third edition of Per Brodal's book "*The central nervous system: structure and function*",

last edited in 1998, attests to the efforts of the author to keep up with the rapid pace of development in the field of neurosciences. Many of us probably remember the repulsive effect of overwhelming details in some textbooks of neuroanatomy or neurophysiology, that fail to be relevant in clinical practice. Here, the dynamic and concise presentation of both the structure and the function of the central nervous system at different levels (molecular, cellular, and systems), with special emphasis on how the different components are connected and interact, manages to captivate the reader. Beside key information on the fundamental background, there are numerous clinical examples that will help the medical student to bridge the gap between basic and clinical neuroscience. The book also offers several didactic drawings and figures, and, for the reader interested in a particular topic, more detailed sections are placed in highlighted boxes. In addition, a rich selection of references recommended by the author on each topic are listed at the end of the book. The third edition includes two new sections on the vestibular system and the control of eye movements.

The principal aim of the author, who perpetuates a familial tradition (the first Norwegian edition of the book was run by Per Brodal's father in 1949), is "to stimulate understanding rather than memorization of isolated facts" and "[to foster] a realistic attitude toward our still limited ability to explain the marvels of the human brain."

I recommend this book to all medical students, and also to more advanced clinicians who wish to refresh their knowledge in basic neurosciences or as a useful tool for teaching their younger colleagues.

S Debette

CORRECTION

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In the Letter by Jardine *et al* (*J Neurol Neurosurg Psychiatry* 2004;**75**:1651) the initials of Krediet were published incorrectly. The correct initials are C T P.