

# PostScript

## LETTERS

### Conduction block in the forearm associated with acute varicella zoster virus infection

We report the case of an adult patient with neurophysiological evidence of persisting conduction block in the forearm segment of the left median nerve and absent responses from the sensory branch of the musculocutaneous nerve (MCN), which had developed during an episode of acute generalised varicella zoster virus (VZV) infection. Clinical manifestations of motor involvement in herpes zoster (HZ) are generally rare and usually due to central nervous system involvement.<sup>1</sup> Motor peripheral nervous system manifestations do exist and have been ascribed to nerve root degeneration due to lymphocytic inflammation and vasculitis with possible spread into the spinal cord.<sup>2</sup> Recently, conduction block has been identified for the first time as the cause of weakness in an immunocompromised patient with HZ, with evidence of extension of VZV infection along the median nerve on magnetic resonance imaging,<sup>3</sup> but persisting conduction block has up to now not been described as a complication of acute VZV infection.

#### Case report

A 29 year old Caucasian electrician was seen for neurophysiological assessment with weakness of his left hand and numbness along the lateral aspect of his left forearm of 9 months' duration. The numbness had developed 9 days into a severe primary attack of chickenpox, which required hospitalisation. The weakness remained unnoticed by the patient until detection during routine follow up. Oral aciclovir had been commenced 3 days after the onset of the acute illness. No intravenous access had been used in the patient's left arm. The past medical history included an anecdotal first primary attack of chickenpox at the age of 4, but was otherwise unremarkable.

Findings on neurological examination were confined to the left arm. There was no muscle wasting or fasciculations and deep tendon reflexes were preserved. Muscle testing revealed weakness in the left hand corresponding to median innervated muscles: abductor pollicis brevis (APB) (4/5), opponens pollicis (4/5), and first and second lumbricals (4/5) (MRC rating scale). In addition, there was hypaesthesia for light touch and pinprick in the territory of the sensory branch of MCN.

Magnetic resonance imaging of both forearms was inconclusive with no evidence of significant signal alteration at the proposed site of the conduction block.

Motor nerve conduction studies revealed partial conduction block in the left median nerve between 9.1 and 11.1 cm above the proximal wrist crease (fig 1) with a reduced forearm velocity (34.6 m/s) and absent F-waves. The elbow mixed median nerve potential was smaller on the left than on the right (15.2 v 33.9  $\mu$ V), thus confirming

the presence of a partial conduction block in the forearm segment of the left median nerve. The sensory nerve action potential for the left sensory branch of MCN was absent with normal amplitudes and velocities from the right. Nerve conduction studies were normal for the right median as well as the ulnar and radial nerves bilaterally. Needle electromyography showed normal motor units with a reduced interference pattern and single fasciculation potentials in left APB and was normal in left first dorsal interosseus, flexor pollicis longus, biceps, and extensor digitorum communis.

#### Comment

Conduction block in acute VZV infection has, to the best of our knowledge, never been described before. Partial infarction of a mixed nerve in vasculitic mononeuritis multiplex can cause conduction block by selectively damaging Schwann cells, although axonotmesis with axonal damage and sensory-motor symptoms in the affected nerve would be more typical and should have been apparent during neurophysiological testing. Both the median nerve and the sensory branch of MCN share fibre supply from cervical nerve roots which later form the lateral cord, and they are often in close anatomical proximity in the arm due to frequent anatomical variations. The simultaneous involvement of the median nerve and the sensory branch of MCN might thus indicate a direct spread of the virus between the two nerves. Alternatively, indirect spread from the purely sensory branch of MCN via the spinal cord might have occurred. Autopsies of nervous tissue from HZ patients have shown VZV DNA and antigen to be present in damaged nerve fibres including motor neurons, suggestive of neuronal spread.<sup>4</sup> Recently, conduction

block in the forearm segment of the median nerve in a case of HZ has speculatively been attributed to local damage of Schwann cells of the motor nerves by direct local invasion or remote allergic mechanisms,<sup>3</sup> although the exact pathophysiology in these cases remains to be established.

The patient was found to have fasciculation potentials but no other forms of spontaneous activity in APB, but in none of the other muscles tested. The observed fasciculation potentials most likely represent axonal hyperexcitability at the site of the conduction block in analogy to the presumed mechanism responsible for the occurrence of single and grouped fasciculation potentials in other neuropathies characterised by persistent conduction block.<sup>5</sup>

U S Raasch, J P Heath

Department of Clinical Neurophysiology, University Hospital of Wales, Cardiff, UK

Correspondence to: Dr U S Raasch, Department of Clinical Neurophysiology, University Hospital of Wales, Cardiff, UK; raaschs@cardiff.ac.uk

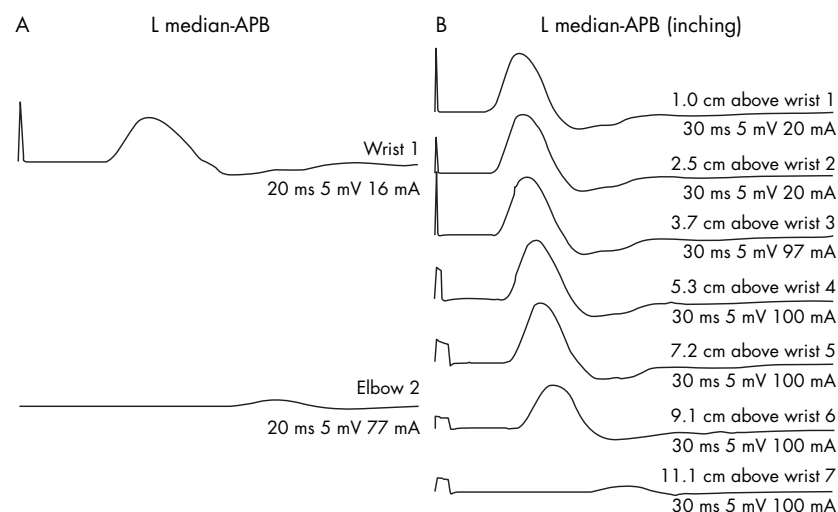
Written confirmation from the Local Research and Ethics Committee in Cardiff was obtained confirming that formal ethical approval was not needed for this case study.

doi: 10.1136/jnnp.2004.059147

Competing interests: none declared

#### References

- Haanpaa M, Hakkinen V, Nurmikko T. Motor involvement in acute herpes zoster. *Muscle Nerve* 1997;20(11):1433–8.
- Gilden DH, Kleinschmidt-DeMasters BK, LaGuardia JJ, et al. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med* 2000;342(9):635–45.



**Figure 1** Left median compound muscle action potentials recorded from abductor pollicis brevis muscle of a patient with previous varicella zoster virus infection and weakness in left median nerve innervated hand muscles. Stimulation sites at wrist and elbow (A) and 1.0, 2.5, 3.7, 5.3, 7.2, 9.1, and 11.1 cm above the proximal wrist crease (B). Gain 5 mV per division, sweep duration 20 ms (A) and 30 ms (B), respectively. Slowing of motor fibres and partial conduction block between 9.1 and 11.1 cm above the proximal wrist crease is demonstrated.

- 3 **Murakami T**, Shibazaki K, Kurokawa K, *et al.* Conduction block of varicella zoster virus neuropathy. *Neurology* 2003;**61**(8):1153–4.
- 4 **Schmidbauer M**, Budka H, Pilz P, *et al.* Presence, distribution and spread of productive varicella zoster virus infection in nervous tissues. *Brain* 1992;**115**(Pt 2):383–98.
- 5 **Roth G**, Magistris MR. Neuropathies with prolonged conduction block, single and grouped fasciculations, localized limb myokymia. *Electroencephalogr Clin Neurophysiol* 1987;**67**(5):428–38.

### Toscana virus causing severe meningoencephalitis in an elderly traveller

Toscana virus (TOSV) is classified in the sandfly fever virus group of arboviruses (family *Bunyaviridae*, genus *Phlebovirus*) along with Sicilian (SFSV) and Neapolitan (SFNV) sandfly fever virus. SFSV and SFNV cause a transient febrile illness, whereas TOSV also causes mild acute aseptic meningitis. In endemic regions TOSV has been identified as an important cause of viral aseptic meningitis among the indigenous population. TOSV is transmitted by the sandfly species *Phlebotomus perniciosus* and *Phlebotomus perfiliewi*. Circulation of TOSV follows the distribution of its vectors—that is, the Mediterranean, Middle East, Western Asia, and North Africa—and the disease coincides with the seasonal life cycle of insect vectors.<sup>1–3</sup> Laboratory confirmation of clinically suspected cases can be carried out by detection of anti-TOSV IgG or IgM antibodies in blood and cerebrospinal fluid (CSF) using different techniques. Direct detection of virus is possible by cell culture or reverse transcriptase polymerase chain reaction (RT-PCR) but will often fail because of the short term nature of the viraemia.

Throughout the last decades there have been increasing numbers of cases of TOSV infection imported into northern Europe from endemic areas. Among other causes, it

therefore now has to be considered in the differential diagnosis of acute aseptic meningitis.<sup>1–2</sup>

#### Case report

Four days after having returned from Malaga, Spain, in July 2004 an 80 year old woman was found in a state of deteriorated consciousness. There was enuresis and encopresis, probably as a result of an epileptic fit. Apart from adult onset diabetes mellitus the patient's medical history was unremarkable.

On admission to hospital, the patient was confused and agitated, with a body temperature of 39.5°C. There was neck rigidity but neurological examination showed no other abnormalities.

Routine clinical chemistry analyses on admission showed slight increases in liver enzymes (aspartate aminotransferase 50 U/l; alanine aminotransferase 87 U/l;  $\gamma$ -glutamyltransferase 93 U/l), erythrocyte sedimentation rate (18 mm/h), and glycated haemoglobin (HbA1c; 7.6%).

Examination of CSF revealed lymphocytic pleocytosis (265 cells/mm<sup>3</sup>) and raised protein (47 mg/dl) and lactate (4.3 mmol/l) (table 1). PCR for herpes simplex virus 1 (HSV1) and HSV2 was negative.

Both CSF and serum samples collected on days 2 and 6 of disease tested negative for antibodies against West Nile and tick born encephalitis virus by immunofluorescence assay (IFA). RT-PCR for TOSV<sup>4</sup> and enterovirus RNA was negative. Infection of *Vero* cells with CSF yielded no cytopathic effect.

Serum and CSF samples collected on days 2, 6, 13, and 27 after admission were examined for the presence of anti-TOSV, anti-SFNV, and anti-SFSV IgG and IgM antibodies. IgG and IgM IFA<sup>5</sup> revealed positive results for both TOSV (strain ISS.Ph1.3 1971) and SFNV (strain Sabin 1985), but anti-SFSV (strain Sabin 1985) antibodies were not found in either serum or CSF samples.

Anti-TOSV IgG titres ranged from 1:640 to 1:10240 in serum and 1:20 to 1:5120 in CSF. IgG levels for SFNV ranged from 1:320 to 1:2560 and from 1:20 to 1:1280, respectively. IFA IgM titres could only be detected in serum, ranging from 1:80 to 1:160 for TOSV and from 1:40 to 1:80 for SFNV.

The presence of a pattern of cross reactivity typical of TOSV infection<sup>2</sup> supported a preliminary diagnosis of acute TOSV encephalitis. For confirmation, the specificity of antibodies was demonstrated by a commercially available TOSV IgG/IgM enzyme immunoassay (EIA) using recombinant antigen (Diesse Diagnostica, Milan, Italy).<sup>5</sup> IFA results for serum samples were confirmed by EIA. Nevertheless, EIA appeared more sensitive than IFA in detecting CSF IgM antibodies (first positive result for CSF IgM in EIA on day 2). In contrast, IgG in CSF samples was only inconsistently detected by EIA (negative results for CSF IgG in EIA on days 2, 13, and 27).

The patient was transferred to the neurological critical care unit and treated empirically with intravenous ceftriaxone, levofloxacin, and aciclovir until diagnosis of TOSV meningoencephalitis was confirmed. Consciousness deteriorated subsequently, leaving the patient in a comatose state for three days. On day three after admission a generalised seizure occurred. Electroencephalography (EEG) showed signs of diffuse encephalopathy with basal activity at 6–7 Hz and symmetrical slow waves. Computed tomography and magnetic resonance imaging of the brain showed diffuse atrophy without evidence of focal lesions. Measurement of TAU protein, S100 protein, and neurone specific enolase in the CSF revealed no signs of neuronal cell damage. Nevertheless, raised  $\beta$ 2-microglobulin levels and oligoclonal banding showed that there was an intrathecal immune reaction (table 1).

Ten days after admission the patient recovered from her comatose state. A slow improvement in her level of consciousness and her general condition was observed subsequently as the fever resolved.

One month after admission CSF and liver enzymes were nearly normal. EEG showed an increase of basal activity to 8 c/s. Slightly impaired cognitive functions could still be observed (mini-mental state examination score 17/30).

#### Comment

Besides Rift Valley fever virus, TOSV is the only member of the Phlebovirus group causing aseptic meningitis. Previously, severe neurological manifestations have been described only occasionally. Within three to six days after infection symptoms such as fever, myalgia, headache, vomiting, and neck rigidity do occur, but a lesser degree of encephalic involvement has generally been reported. As in other viral meningitides, symptoms of aseptic meningitis related to TOSV infection disappear completely within a few days. Asymptomatic infections and infections without CNS involvement also occur.<sup>1–3</sup>

The brain involvement in this case caused a severe, long lasting impairment of consciousness, seizures as an unusual clinical manifestation, and a prolonged convalescence period. Seldom reported before, raised liver enzymes can be interpreted as a sign of a systemic infection with involvement of the liver.

**Table 1** Results of cerebrospinal fluid and serum sample analysis after admission (as far as we know this is the first time that markers of cell damage and immune reaction have been measured in a patient with acute toscana virus meningoencephalitis)

	Reference range	Day 2	Day 6	Day 13	Day 27
WBC count (cells/mm <sup>3</sup> )	0 to 5	265	60	30	16
Lactate (mmol/l)	1.1 to 2.2	4.3	3.1	2.5	2.2
Glucose (mmol/l)	2.78 to 4.16	7.33	6.16	4.88	4.50
Total protein (mg/dl)	15–45	47	32	25	28
Oligoclonal banding	Negative	Negative	One band	Negative	Negative
Tau protein (pg/ml)	<350	194	NA	191	332
$\beta$ 2-Microglobulin (mg/l)	<2	NA	5	3.2	3.1
Neurone specific enolase (ng/ml)	<12.5	8.2	7.5	5.3	7.1
S-100 protein (pg/ml)	<2300	NA	1030	NA	644
Anti-TOSV antibodies in CSF					
IgG IFA	<1:10	1:20	1:80	1:2560	1:5120
IgM IFA	<1:10	<1:10	<1:10	<1:10	<1:10
IgG EIA	–	–	+	–	–
IgM EIA	–	+	+	+	+
Anti-TOSV antibodies in serum					
IgG IFA	<1:10	1:640	1:2560	1:5120	1:10240
IgM IFA	<1:10	1:80	1:320	1:160	1:160
IgG EIA	–	+	+	+	+
IgM EIA	–	+	+	+	+

CSF, cerebrospinal fluid; EIA, enzyme immunoassay; IFA, immunofluorescence assay; NA, not assessed; WBC, white blood cell.

Owing to the large variety of pathogens causing acute aseptic meningitis, clinicians rely on rapid laboratory confirmation of suspected cases by standard methods such as RT-PCR or the plaque reduction neutralisation test (PRNT). Nowadays, PRNT is rarely used owing to its complexity and time consuming nature, while RT-PCR appears inadequate because of the short duration of the viraemia.<sup>1,2</sup> Recently developed EIA formats can establish the presence of infection by detecting specific IgM in acute phase samples and were able to confirm TOSV infection in this case. With millions of travellers and increasing TOSV infections around the Mediterranean basin, commercially available EIA methods will be of growing importance. In addition to other severe travel related diseases, TOSV infections now need to be considered by physicians.

**J Kuhn, H Bewermeyer, U Hartmann-Klosterkoetter**

Department of Neurology, Kliniken der Stadt Köln, Krankenhaus Merheim, Cologne, Germany

**P Emmerich, S Schilling**

Bernhard Nocht Institute For Tropical Medicine, Department of Virology, Hamburg, Germany

**M Valassina**

University of Siena, Department of Molecular Biology, Microbiology Section, Laboratory of Virology, Siena, Italy

Correspondence to: Dr Jens Kuhn, Department of Neurology, Kliniken der Stadt Köln, Krankenhaus Merheim, Ostmerheimerstrasse 200, 51109 Cologne, Germany; Kuhnj@kliniken-koeln.de; JKuhn11@aol.com

doi: 10.1136/jnnp.2004.060863

Competing interests: none declared

## References

- 1 Valassina M, Cusi MG, Valensin PE. A Mediterranean arbovirus: the Toscana virus. *J Neurovirol* 2003;**9**:577–83.
- 2 Dionisio D, Esperti F, Vivarelli A, et al. Epidemiological, clinical and laboratory aspects of sandfly fever. *Curr Opin Infect Dis* 2003;**16**:383–8.
- 3 Echevarria JM, de Ory F, Guisasaola ME, et al. Acute meningitis due to Toscana virus infection among patients from both the Spanish Mediterranean region and the region of Madrid. *J Clin Virol* 2003;**26**:79–84.
- 4 Valassina M, Valentini M, Valensin PE, et al. Fast duplex one-step RT-PCR for rapid differential diagnosis of enterovirus or toscanovirus meningitis. *Diagn Microbiol Infect Dis* 2002;**43**:201–5.
- 5 Soldateschi D, dal Maso GM, Valassina M, et al. Laboratory diagnosis of Toscana virus infection by enzyme immunoassay with recombinant viral nucleoprotein. *J Clin Microbiol* 1999;**37**:649–52.

## Intracerebral haemorrhage in CADASIL

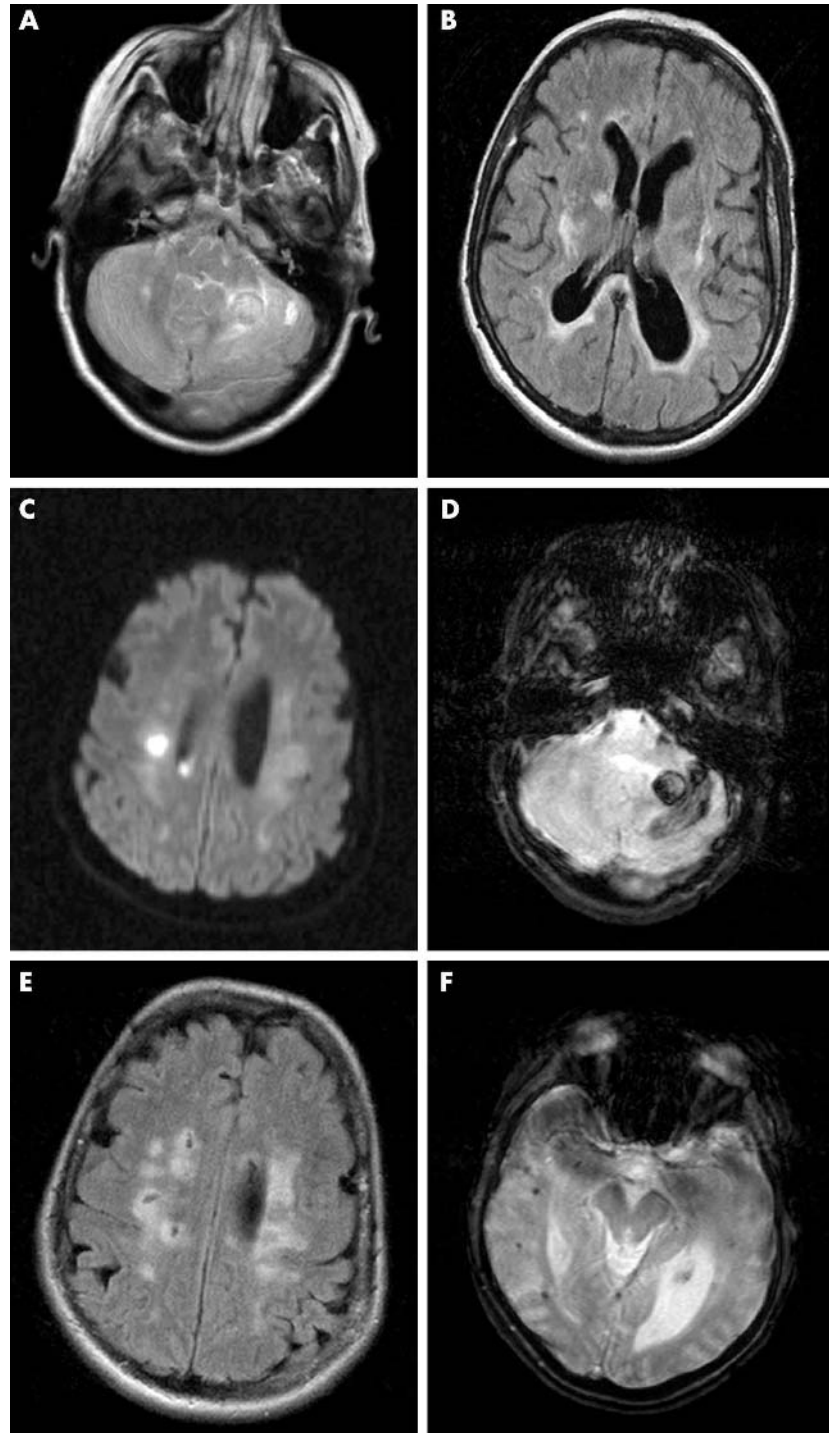
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL) is a rare hereditary disease characterised by recurrent transient ischaemic attacks, strokes, and vascular dementia. Pathological studies reveal multiple small infarcts and diffuse white matter changes as well as vascular alterations most prominent in small arteries.<sup>1</sup> The presence of granular osmiophilic material in arterial walls on ultrastructural examination is pathognomonic. Mutations in the notch3 gene located on chromosome 19 are associated with the

disease.<sup>2</sup> Here we report a patient with an unusual clinical course with recurrent intracerebral haemorrhage.

## Case report

A 47 year old woman was admitted after a fall at home, followed by several minutes of unconsciousness. Her past medical history

was uneventful. In particular, there was no history of migraine or depression, and she was not taking any drugs. On admission, her husband reported memory deficits for several weeks. Initially, the patient complained about headaches and mild dysarthria. Moderate left sided hemiparesis and pronation of the left arm were present. Blood pressure was raised to 220/120 mm Hg



**Figure 1** Bleeding in the left cerebellar hemisphere as shown in pd+T2 tse (A) and T2\* (D). White matter lesions in the FLAIR sequence (B, E); note the lesions in the external capsule which are often present in CADASIL (B). (C) Acute ischaemic lesions in the right hemisphere in a diffusion weighted image. (F) Multiple microbleeds shown in T2\*. CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; FLAIR, fluid attenuated inversion recovery.

without a known history of arterial hypertension. Neuropsychological deficits were prominent in impaired semantic, visual-spatial, and episodic memory, and in deterioration in cognitive speed. Concentration and mathematical problem solving were also reduced, indicating severe cognitive impairment. Initial cranial computed tomography revealed a haemorrhage of 20 mm diameter in the left cerebellar hemisphere. Subsequent magnetic resonance imaging (MRI) with T2\* gradient echo (GE) showed more than 25 small haemorrhages distributed over the entire brain. T2 weighted scans showed white matter lesions with periventricular emphasis (fig 1). Serum markers for vasculitis and coagulation indices were normal, as was the cerebrospinal fluid. An ophthalmological examination showed hypertensive changes. Ultrasound sonography of the extracranial and intracranial vessels revealed arteriosclerotic vessel walls but no stenosis. Electronmicroscopic examination of a skin biopsy showed granular osmiophilic material (GOM) in the basal lamina of small arterioles, establishing the diagnosis of CADASIL. Direct bidirectional sequencing of all exons coding for epidermal growth factor (EGF)-like repeat domains (exons 2 to 24) of *notch3* did not reveal any mutation.

After stepwise normalisation of arterial blood pressure, the patient gradually improved over the following weeks. Headaches, ataxia, and dysarthria resolved gradually, but severe neuropsychological deficits remained, rendering her unable to take care for herself. A follow up examination three months after discharge showed further amelioration of gait without any other focal neurological symptoms. The neuropsychological deficits had improved slightly, but there were still severe memory deficits. The patient was aware of these deficits and she reacted in a depressive manner. Activities of daily life were moderately impaired. Follow up MRI showed no new lesions.

## Comment

The clinical course of this case with intracerebral bleeding in combination with excessive blood pressure values was consistent with hypertensive intracerebral haemorrhage. Although there was no history of known arterial hypertension, the changes of the retina supported this diagnosis. Hypertension is the most common cause of intracerebral haemorrhage, accounting for 50–70% of cases. Hypertensive bleeding into the cerebellum, however, is relatively rare (<10%). The finding of numerous cerebral microbleeds on T2\*-GE MRI led to the suspicion of amyloid angiopathy, a common cause of intracerebral haemorrhage in the elderly. On the other hand, the relatively young age of the patient and the family history (mother and two sisters suffering from migraine; father died at 47 years from unknown cause) was compatible with an autosomal dominantly inherited condition, for example, CADASIL. The finding of GOM in the basal lamina of small vessels is pathognomonic of this disease and confirmed the diagnosis. Mutations in exons 2 to 24 of the *notch3* gene are found in approximately 95% of patients, but were not detected in this case.<sup>2</sup>

While transient ischaemic attacks and ischaemic strokes, along with the development of vascular dementia, are common, major intracerebral haemorrhages are not a

common feature of CADASIL. There have been sporadic reports of intracerebral haemorrhages,<sup>4,5</sup> but the significance of these observations remains unclear, given the absence of intracerebral haemorrhage in large patient series.<sup>6,7</sup> In a recent study with GE T2\* weighted scans, microbleeds (up to 22 in a single subject) ranging from 2 to 10 mm in diameter were found in 69% of CADASIL patients examined, but no major ICH was found.<sup>8</sup> Another study found microbleeds in 31% of all CADASIL patients examined, and an increased risk of intracerebral haemorrhage was predicted. The presence of microbleeds correlated with age and the use of antiplatelet drugs.<sup>9</sup> CADASIL leads to degeneration of small arterioles, thus increasing the probability of vessel rupture in arterial hypertension. Compared with the patients in the studies cited above, our patient showed even more microbleeds (25), possibly indicating a greater risk of intracerebral haemorrhage in patients with CADASIL in combination with arterial hypertension. While the white matter pathology in our patient may appear relatively sparse, lesions in the external capsule and the temporal lobe typical of CADASIL were present.

We conclude that CADASIL should be considered in patients with cerebral haemorrhage, and careful blood pressure management is particularly important in CADASIL patients, as the risk of vessel rupture and subsequent intracerebral haemorrhage appears to be further increased compared with patients with arterial hypertension alone. While there is no effective treatment for CADASIL, control of arterial hypertension could at least slow the rate of deterioration in this disabling and dementing disorder.

**A Ragoschke-Schumm, H Axer, O W Witte, S Isenmann**

Department of Neurology, Hans-Berger-Kliniken, Friedrich-Schiller-University Jena, Jena, Germany

**C Fitzek**

Department of Diagnostic and Interventional Radiology, Friedrich-Schiller-University Jena

**M Dichgans, N Peters**

Department of Neurology, Klinikum Grosshadern, Ludwig-Maximilians-University, Munich, Germany

**J Mueller-Hoecker**

Department of Pathology, Ludwig-Maximilians-University

Correspondence to: Dr med Andreas Ragoschke-Schumm, Department of Neurology, Friedrich-Schiller-University Jena, Erlanger Allee 101, D-07747 Jena, Germany; andreas.ragoschke-schumm@med.uni-jena.de

doi: 10.1136/jnnp.2004.059212

Competing interests: none declared

## References

- 1 **Tournier-Lasserre E, Joutel A, Melki J, et al.** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy maps to chromosome 19q12. *Nat Genet* 1993;**3**:256–9.
- 2 **Peters N, Opherk C, Bergmann T, et al.** Spectrum of mutations in biopsy-proven CADASIL: implications for diagnostic strategies. *Arch Neurol*, (in press).
- 3 **Joutel A, Corpechot C, Ducros A, et al.** Notch3 mutations in CADASIL, a hereditary adult-onset disease condition causing stroke and dementia. *Nature* 1996;**383**:707–10.
- 4 **Baudrimont M, Dubas F, Joutel A, et al.** Autosomal dominant leukoencephalopathy and

subcortical ischemic stroke: a clinicopathological study [abstract]. *Stroke* 1993;**24**:122–5.

- 5 **Sourander P, Walinder J.** Hereditary multi-infarct dementia: morphological and clinical studies of a new disease. *Acta Neuropathol (Berl)*, 1977;**39**:247–54.
- 6 **Dichgans M, Mayer M, Utner I, et al.** The phenotypic spectrum of CADASIL: clinical findings in 102 cases. *Ann Neurol* 1998;**44**:731–9.
- 7 **Chabriat H, Vahedi K, Iba-Zizen MT, et al.** Clinical spectrum of CADASIL: a study of 7 families: cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. *Lancet* 1995;**346**:934–9.
- 8 **Dichgans M, Holtmannspötter M, Herzog J, et al.** Cerebral microbleeds in CADASIL. A gradient-echo magnetic resonance imaging and autopsy study. *Stroke* 2002;**33**:67–71.
- 9 **Lesnik Oberstein SAJ, Van den Boom R, Van Buchem MA, et al.** Cerebral microbleeds in CADASIL. *Neurology* 2001;**57**:1066–70.

## Catastrophic primary antiphospholipid syndrome presenting as status epilepticus

Antiphospholipid syndrome (APS) is defined as the occurrence of arterial or venous thrombosis or recurrent miscarriage, with raised titres of antiphospholipid antibodies, namely lupus anticoagulant (LA) or anticardiolipin antibodies (aCL). An accelerated form of APS is catastrophic antiphospholipid syndrome (CAPS) or Asherson's syndrome. Proposed diagnostic criteria for definite CAPS are: multiorgan failure, development of manifestations within 1 week, demonstration of antiphospholipid antibodies and histopathological evidence of microthrombosis (positive predictive value 99.4%).<sup>1</sup> Precipitants include infection, surgery, and childbirth. Patients typically develop widespread thrombotic vasculopathy with marked thrombocytopenia. Clinically apparent cerebral infarction occurs much less frequently than in uncomplicated APS but the major pathological manifestation of CAPS is cerebral microthrombosis at postmortem examination.

## CASE REPORT

A 30 year old woman delivered her first child following a full term uncomplicated pregnancy. Three weeks later, she developed headache and transient hemiparesis. The following day she had an episode of speech arrest, bit her tongue, and held both arms stiffly in the air for about 1 minute. On admission to hospital, she was pyrexial and developed generalised tonic clonic seizures. There was no relevant previous medical history and she was not taking any medication. Blood tests, including erythrocyte sedimentation rate (ESR) and C reactive protein (CRP), were normal. Computed tomography scan of the brain and analysis of the cerebrospinal fluid (CSF) were normal. Gynaecological examination showed no retained products of conception. The seizures proved refractory to treatment with intravenous lorazepam. She was transferred to a specialist neurological centre that day.

On arrival she was agitated, disorientated and pyrexial (38°C). Generalised tonic clonic seizures continued. Neurological examination was normal except that all limb reflexes were pathologically brisk and plantar responses were extensor. General examination was unremarkable. Despite being given "loading" doses of phenytoin, phenobarbitone, and magnesium sulphate, the seizures continued. She was anaesthetised and intubated, and mechanical ventilation was introduced.

Treatment with high dose intravenous aciclovir for presumed viral encephalitis was commenced.

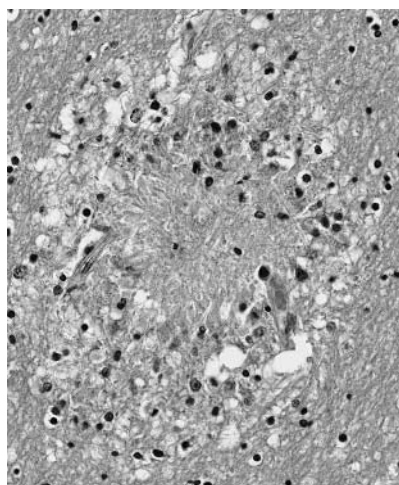
Investigations revealed a normal full blood count and film with a platelet count of  $267 \times 10^9/l$ . ESR and CRP were mildly raised at 46 mm/h (normal 1–20) and 28.7 mg/l (normal 0–5). Serial measurements of platelet count, ESR, and CRP did not show any significant change throughout the illness. All other blood tests including coagulation screen were normal or negative.

Magnetic resonance imaging of the brain was normal with no evidence of venous sinus thrombosis, cerebral infarction or haemorrhage. A second lumbar puncture revealed an opening pressure of 30 cm H<sub>2</sub>O. CSF analysis showed clear colourless fluid with 4 lymphocytes/mm<sup>3</sup>, a red cell count of  $<1/mm^3$ , total protein of 0.36 g/l and a CSF:plasma glucose ratio of 4.4:8.9 mmol/l. CSF and serum oligoclonal bands were negative. Multiplex PCR for CSF herpes was negative.

EEG confirmed a diffuse encephalopathic process with unequivocal epileptiform activity over the frontal regions bilaterally with some periodic complexes more prominent on the left. A thrombophilia screen was performed during her illness but results were not available until after her death, and revealed the presence of lupus anticoagulant. Immunological assay for aCL was negative.

Whenever anaesthesia was reduced, seizure activity returned and her pyrexia persisted with no identifiable microbiological source. On day 7 her condition suddenly deteriorated with marked acidosis (base deficit of -14), renal failure, and haemodynamic instability. She received inotropic support and haemofiltration for presumed septic shock. She suffered a cardiac arrest <24 hours later and died despite prolonged efforts at resuscitation.

A postmortem examination revealed small vessel fibrin thrombi in the brain (fig 1). There was no evidence of large vessel cerebral thrombosis. The heart showed multifocal haemorrhages with surrounding muscle degeneration, and the lungs showed widespread small vessel thrombosis and shock lung. There was acute tubular necrosis of the kidneys, bilateral adrenal haemorrhage, and hepatic centriacinar degeneration.



**Figure 1** Cerebral white matter small vessel showing necrosis and perivascular microgliosis following occlusion by thrombus.

## DISCUSSION

This patient developed a thrombotic microangiopathy (TMA) 1 month after a normal term delivery. The premortem laboratory investigations and postmortem examination revealed she was suffering from APS. The alternative postpartum TMA diagnosis of thrombotic thrombocytopenic purpura was excluded by the fibrin nature of the thrombi and the normal platelet count.

CAPS occurs in <1% of patients with APS.<sup>2</sup> However, it is vital to be aware of the diagnosis as patients rapidly develop severe multisystem failure. A review of the pathogenesis of 80 cases of CAPS noted an excess of women (79%) with an average age at onset of 37 years.<sup>3</sup> The majority with multiorgan failure had secondary APS, mostly associated with systemic lupus erythematosus. Obstetric complications are recognised precipitants of CAPS, probably because of increases in levels of natural clotting factors. Two cases of CAPS occurring in the postpartum period have been reported, both following fetal loss.<sup>4,5</sup>

Cerebral involvement has been reported in around 60% of cases of CAPS.<sup>3</sup> However, there are no previous reports of primary antiphospholipid syndrome presenting with status epilepticus. The case was unusual in several other respects. There was no previous diagnosis of APS and no history of miscarriages or thrombotic events. The patient presented with isolated neurological symptoms with no evidence of other organ involvement until 7 days later. Daily blood tests did not raise the suspicion of thrombophilia or blood dyscrasia and, in contrast to a series of 80 patients in whom 98% had high aCL titres,<sup>3</sup> this patient had negative aCL.

The optimal treatment for CAPS is uncertain but the rationale is to prevent ongoing thrombosis with anticoagulation and to prevent production of mediators that generate the hypercoagulable state by immunosuppression. A review of data from the international CAPS registry found that patients who received the combination of anticoagulation plus steroids plus plasma exchange or intravenous immunoglobulin had the best survival rate (63%).<sup>1</sup>

This case emphasises that CAPS may present as an apparently isolated cerebral disorder. It is important to maintain a high degree of suspicion of antiphospholipid syndrome in critically unwell patients, particularly with known precipitating factors for CAPS such as during the postpartum period. Early treatment with anticoagulation and immunosuppression gives the best chance of improving the >50% mortality rate of the condition.

**L J Coward, D M Kullmann**

Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

**L J Coward, N P Hirsch, R S Howard**

Harris Neuromedical Intensive Care Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London, WC1N 3BG, UK

**S B Lucas**

GKT/GST Dept of Pathology, St Thomas' Hospital, Lambeth Palace Road, London, SE17EH, UK

Correspondence to: Dr R S Howard, Box 33 Medical Intensive Care Unit, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG; robin.howard@talk21.com

doi: 10.1136/jnnp.2005.066746

Competing interests: none

## REFERENCES

- 1 **Cervera R**, Font J, Gomez-Puerta JA, Espinosa G, Cucho M, Bucciarelli S, Ramos-Casals M, Ingelmo M, Piette JC, Shenfeld Y, Asherson RA, members of the CAPS Registry Project Group. Validation of the preliminary criteria for the classification of catastrophic antiphospholipid syndrome. *Ann Rheum Dis*. 2005; doi: 10.1136/ard.2004.025759 (Epub).
- 2 **Asherson RA**, Espinosa G, Cervera R, et al. Catastrophic antiphospholipid syndrome. Proposed guidelines for diagnosis and treatment. *J Clin Rheumatol* 2002;**8**:157–65.
- 3 **Asherson RA**, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome: clues to the pathogenesis from a series of 80 patients. *Medicine (Baltimore)* 2001;**80**:355–77.
- 4 **Hochfeld M**, Druzin ML, Maia D, et al. Pregnancy complicated by primary antiphospholipid syndrome. *Obstet Gynecol* 1994;**83**:804–5.
- 5 **Kupferminc MJ**, Lee MJ, Green D, et al. Severe postpartum pulmonary, cardiac and renal syndrome associated with antiphospholipid antibodies. *Obstet Gynecol* 1994;**83**:806–7.

## Use of mirror dystonia as guidance for injection of botulinum toxin in writing dysfunction

The successful application of botulinum toxin (BTX) injections in the treatment of focal hand dystonia is largely dependent on careful evaluation and selection of muscles to be injected.<sup>1</sup> It has been suggested that patients should be examined for abnormal postures at rest and while carrying out the affected task in question as well as other tasks (such as using a cup or a comb).<sup>2</sup> Simple techniques such as the localisation of subjective pain and fatigue accompanied by palpation of the area of discomfort can also be used.<sup>2</sup>

Mirror dystonia consists of dystonic postures and movements of the dominant hand while writing or performing other tasks with the non-dominant hand.<sup>3</sup> We present a series of six patients who were successfully injected with BTX using mirror dystonia as an additional tool for muscle evaluation.

We carried out a retrospective review of the case records of consecutive patients with writing dysfunction (writer's cramp and writing tremor) who had been injected with BTX type A (Botox®, Allergan Pharmaceuticals, Irvine, California, USA) between November 2000 and October 2002 at our movement disorders clinic. Our study was limited to patients with writing dysfunction who displayed mirror dystonia while writing with their non-dominant hand. We specifically examined patients for mirror dystonia by asking them to write with their non-dominant hand while resting the dominant hand on the ulnar side of the forearm (unaware of our focus on the detection of mirror dystonia of the resting limb). Patients were injected under EMG guidance, using an Allergan® EMG needle. We recorded the muscles injected and the dose each muscle received. Peak effect was defined as the maximum benefit obtained from the injection. It was rated on a 0 to 3 global impression scale (0 = no effect; 1 = mild improvement; 2 = moderate improvement; 3 = marked improvement). The presence and severity of adverse events was also recorded. We also looked at the concordance between observation of the dominant limb in the action of writing and

**Table 1** Demographic variables, clinical features, and response to botulinum toxin treatment in our series of patients with writing dysfunction associated with mirror dystonia

Case	Sex	Age	Duration	Type	Mirror dystonia	Muscles selected (dose)	Benefit	Adverse effects
1	F	75	13 years	WC	Flexion of thumb and index finger	R FPL 12.5 U R FDS 12.5 U	Marked	None
2	F	42	8 years	WC	Dorsiextension of thumb, index finger and wrist	R EPL 7.5 U	Marked	None
3	F	48	3 years	WT	Dorsiextension of fingers (not thumb) and wrist	R ECU 10 U R EDC 10 U R FCU 10 U (*)	Moderate	Transient (one month) weakness of extension of 2nd, 3rd, and 4th digits
4	M	38	2 year	WT	Hyperextension of the thumb	R APL 10 U	Moderate	Transient (one week) weakness of dorsiextension of the wrist
5	F	30	11 years	WC	Dorsiextension of index finger	R EIP 10 U	Marked	Transient (2 weeks) weakness of dorsiextension of finger (and milder weakness of extension of the thumb)
6	F	43	6 years	WC	Flexion of wrist and fingers	R FCR 12.5 U R FCU 12.5 U	Mild	Weakness lifting objects

\*Patient injected in FCU owing to discomfort in the volar aspect of the forearm

APL, abductor pollicis longus; ECR, extensor carpi radialis; ECU, extensor carpi ulnaris; EDC, extensor digitorum communis; EIP, extensor. indicis propius; EPL, extensor pollicis longus; FCR, flexor carpi radialis; FCU, flexor carpi ulnaris; FDS, flexor digitorum superficialis; FPL, flexor pollicis longus; L, left; R, right; WR, writer's cramp, WT, writing tremor.

observation of the mirror dystonia movements of the same limb while writing with the non-dominant hand. The formulation and preparation of BTX was carried out using standard methods. Overviews of the demographic, clinical, and treatment variables are presented in table 1. We identified six patients with writing dysfunction (M/F:1/5, mean age 46 years (range 30 to 75), mean duration of disease 7.16 years (range 2 to 13)). Four patients (cases 1, 2, 5, and 6) had writer's cramp and two (cases 3 and 4) had features overlapping writing tremor with writer's cramp. Three patients reported marked (cases 1, 2, and 5), two moderate (cases 3 and 4), and one mild improvement (cases 6). We further identified two subgroups: four patients where mirror dystonia consisted of any combination of extension/abduction of the thumb, fingers, and wrist (subgroup A: cases 2, 3, 4, and 5) and two patients where mirror dystonia consisted of hyperflexion of wrist or thumb and fingers (subgroup B: cases 1 and 6). In subgroup A two patients experienced marked improvement and two had moderate improvement following injections. Two of these four patients did not show mirror dystonia movements when seen 15–17 weeks later at the time they were due for repeat injections. In subgroup B one patient experienced marked improvement and one mild improvement. None of our patients had evidence of mirror dystonia in the non-dominant hand when writing with the dominant hand. Regarding adverse events, transient weakness was experienced by four patients (for one to four weeks). No other adverse events were reported.

Concordance in the action of writing and observation of the mirror dystonia movements in the same limb was found in four patients. In three there was enrichment of the observation in that additional muscles could be shown to be active. The two

discordant patients had writing tremor with no overt deviation noted when the dominant hand wrote.

The importance of recognition of mirror dystonia in patients with writing dysfunction has been previously highlighted by Jedynak *et al.*<sup>3</sup> He reported that 29 of 65 patients with writer's cramp had evidence of mirror dystonia and suggested that mirror dystonia may be useful in muscle selection (it may help in the differentiation between primary and compensatory movements). Borgohain *et al* also reported on the subject; however, that work has only been published in abstract form.<sup>4</sup> The investigators proposed that mirror dystonia used as a guide for muscle selection for BTX injections may reduce the difference in outcome between extensor and flexor writer's cramp and suggested that mirror dystonia was a superior method for muscle selection compared with compensatory movements.

Although the mechanism of mirror dystonia remains unclear it has been suggested that it is likely to be related to the metabolic abnormalities shown to involve the primary sensorimotor and supplementary motor cortices in patients with focal hand dystonia.<sup>5</sup> Magnetic cortical stimulation has confirmed that corticocortical inhibition is reduced over both hemispheres.<sup>6</sup> Jedynak *et al* suggested that mirror dystonia is the consequence of abnormal cortical inhibition and decreased selectivity of muscle patterns for highly skilled manual tasks.<sup>3</sup>

We conclude that analysis of the pattern of dystonic posturing displayed in mirror dystonia when examining patients with writing dysfunction is a useful guide for selection of muscles to be injected with BTX. A prospective trial of BTX injections in muscles selected through analysis of mirror dystonia could provide further information about the therapeutic results of this method.

## Acknowledgements

This work was presented in part at the American Academy of Neurology 55th Annual Meeting in Honolulu, Hawaii, 31 March to 4 April 2003.

C Singer, S Papapetropoulos

Department of Neurology, University of Miami School of Medicine, Miami, Florida, USA

L Vela

Fundación Hospital Alcorcón. Alcorcón, Madrid, Spain

Correspondence to: Dr Carlos Singer, Associate Professor of Neurology, University of Miami, School of Medicine, 1501 NW 9th Avenue, Miami, FL 33136, USA; csinger@med.miami.edu

doi: 10.1136/jnnp.2004.062265

Competing interests: none declared

## References

- 1 Karp BI. Botulinum toxin treatment of occupational and focal hand dystonia. *Mov Disord* 2004;**19**(suppl 8):S116–19.
- 2 Karp BI, Hallett M. Botulinum toxin treatment of focal hand dystonia. In: Jankovic J, Hallett M, eds. *Therapy with botulinum toxin*. New York: Marcel Dekker, 1994:299–306.
- 3 Jedynak PC, Tranchant C, de Beyer DZ. Prospective clinical study of writer's cramp. *Mov Disord* 2001;**16**:494–9.
- 4 Borgohain R, Kanikannan MA, Sattaluri S, *et al*. Mirror dystonia (mirror movements) in writer's cramp and therapeutic outcome with botulinum toxin: a prospective study [abstract]. *Mov Disord* 2002;**17**(suppl 5):S293.
- 5 Tempel LW, Perlmuter JS. Abnormal cortical responses in patients with writer's cramp. *Neurology* 1993;**43**:2252–7.
- 6 Ridding MC, Sheehan G, Rothwell JC, *et al*. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry* 1995;**59**:493–8.

## Drug induced pseudolymphoma secondary to ethosuximide

Ethosuximide is an antiepileptic succinimide, widely used in the treatment of absence seizures. Haemopoietic complications associated with the administration of this drug have included leucopenia, agranulocytosis, pancytopenia with or without bone marrow suppression, and eosinophilia.<sup>1</sup> We report a patient with pseudolymphoma induced by ethosuximide, a complication never reported previously.

### Case report

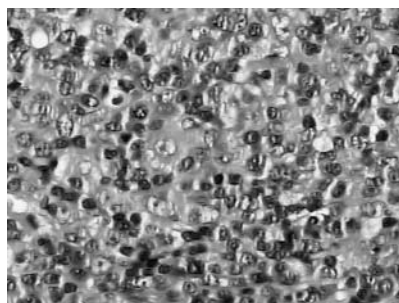
A 12 year old boy presented with a two months history of fever, weight loss (3 kg), and non-painful swellings on the neck, axillae, and both inguinal regions. The patient had been on ethosuximide for three months for childhood absence epilepsy. It was being given at a dose of 30 mg/kg/day, in three divided doses, and the seizures had been under reasonable control.

Physical examination on presentation revealed enlarged lymph nodes on the both sides of the neck, axillae, and inguinal regions. All the nodes were non-tender, firm, measuring 1 to 2 cm in diameter, and freely mobile. The liver and spleen were not palpable and all other systems were normal.

A full blood count revealed a leucopenia of  $3.6 \times 10^3 / \mu\text{l}$  (48% neutrophils, 3% eosinophils, 40% lymphocytes, and 9% monocytes) and a decreased platelet count of  $119.0 \times 10^3 / \mu\text{l}$ . Studies for serological markers revealed no acute or chronic infection with cytomegalovirus, Epstein-Barr virus, herpes simplex virus, or toxoplasmosis.

An excisional biopsy of a 2 cm cervical node was done. Frozen section diagnosis was consistent with lymphoma. Permanent sections showed a diffuse polymorphic lymphoid hyperplasia with effacement of the normal architecture; there was an admixture of lymphoid cells, including small and large lymphocytes and plasma cells (fig 1). Leucocyte phenotyping, using the ABC immunohistochemical method, showed heterogeneous T cell and B cell populations: T cell subsets included CD45RO and CD30. B lymphocyte markers included CD20.

One day after ethosuximide discontinuation the fever disappeared. The lymph nodes were noticed to have decreased in size on the second week and completely regressed on the end of the second month. The leucocyte and platelet counts normalised after two weeks of ethosuximide withdrawal. Positive



**Figure 1** Lymph node biopsy resembles lymphoma, but leucocyte phenotyping shows heterogeneous cell population typical of lymphoid hyperplasia.

rechallenge resulted in drug induced fever and enlargement of the lymph nodes after one week of ethosuximide administration.

### Comment

Lymphadenopathy has been recognised as a complication of drug treatment, particularly with antiepileptic drugs, since the first report of phenytoin-induced pseudolymphoma in 1940.<sup>2</sup> Since then, this idiosyncratic reaction has also been described with carbamazepine, lamotrigine, nifedipine, thioridazine, atenolol, amiloride/hydrochlorothiazide, mexiletine, penicillamine, captopril, enalapril, and methotrexate.<sup>3</sup> Most of these are associated with cutaneous pseudolymphomas, but the antiepileptic drugs are more likely to precipitate cervical lymphadenopathy.

Pathologically, the term "pseudolymphoma" has been used to describe lymphoid cell proliferation with effacement of nodal architecture, so that there is a false appearance suggestive of malignancy. Although the precise pathogenesis of this drug reaction is unknown, pseudolymphoma may develop as a hypersensitivity reaction when a drug or one of its structural ligands acts as an antigen, triggering an immune reaction. Alternatively, the drug in question may promote a dysregulated immune response to another drug or non-pharmacological antigen.<sup>4</sup>

Ethosuximide is widely used in the treatment of absence seizures. On the basis of more than a decade of studies on its cellular effects, the mechanisms of action are thought to include blockade of the low threshold, T-type  $\text{Ca}^{2+}$  current and a reduction in both the non-inactivating  $\text{Na}^{+}$  current and the  $\text{Ca}^{2+}$  activated  $\text{K}^{+}$  current in thalamic and cortical neurones.<sup>4</sup>

The most common dose related side effects are gastrointestinal complaints (nausea, vomiting, and anorexia) and central nervous system (CNS) effects (drowsiness, lethargy, euphoria, dizziness, headache, and hiccup). Some tolerance to these effects develops. Parkinson-like symptoms and photophobia have been also reported. Urticaria and other skin reactions, including Stevens-Johnson syndrome, as well as systemic lupus erythematosus, eosinophilia, leucopenia, thrombocytopenia, pancytopenia, hepatic dysfunction, and aplastic anaemia, also have been attributed to ethosuximide.<sup>1</sup>

In this case, the disappearance of lymphadenopathy with withdrawal of the drug, and its prompt reappearance when the drug was reintroduced, suggests a strong cause-effect association between ethosuximide and lymphadenopathy. To our knowledge, this is the first case report of ethosuximide induced pseudolymphoma and the second to report lymphadenopathy as an adverse effect of ethosuximide.<sup>5</sup>

**M R Masruha, C M Marques, L C P Vilanova**  
Department of Neurology and Neurosurgery, Federal University of São Paulo, São Paulo, Brazil

**M T de Seixas Alves**  
Department of Pathology, Federal University of São Paulo

**M F P Peres**  
Research and Teaching Institute, Albert Einstein Hospital, São Paulo

**M G Rodrigues**  
Department of Paediatrics, Federal University of Espírito Santo, Espírito Santo, Brazil

Correspondence to: Dr Marcelo Rodrigues Masruha, Division of Child Neurology, Department of Neurology and Neurosurgery, Botucatu Street 720, Federal University of São Paulo, São Paulo 04023-9000, Brazil; mmasruha@ig.com.br

doi: 10.1136/jnnp.2005.064923

Competing interests: none declared

### References

- 1 **McCabe PH.** New anti-epileptic drugs for the 21st century. *Expert Opin Pharmacother* 2000;1:633-74.
- 2 **Cooper R, Burrows RGR.** Treatment of epilepsy with sodium diphenylhydantoinate. *Lancet*, 1940;i, 490-2.
- 3 **Pathak P, McLachlan RS.** Drug-induced pseudolymphoma secondary to lamotrigine. *Neurology* 1998;50:1509-10.
- 4 **Jeng YM, Tien HF, Su IF.** Phenytoin-induced pseudolymphoma: reevaluation using modern molecular biology techniques. *Epilepsia* 1996;37:104-7.
- 5 **Ojinnaka NC, Iløje SO.** Ethosuximide induced lymphadenopathy – a case report. *Cent Afr J Med* 2001;47:18-19.

## BOOK REVIEW

### Imitators of Epilepsy, Second Edition

Edited by Peter W Kaplan, Robert S Fisher. New York: Demos Medical Publishing, 2004, \$99.00 (hardcover), pp 296. ISBN 1-888799-83-8

This 300 page hardcover work encompasses four sections: one on general considerations relevant to the topic with specific focus to epileptic versus non-epileptic diagnostic dilemmas; the second section presents different types of non-epileptic spells according to age of presentation; the third section describes other disorders that resemble epileptic seizures such as migraine, vestibular problems, movement disorders, hyperplexia, and startle disorders; and the fourth section focuses on cephalopathies, neuro-endocrine, metabolic and toxic conditions imitating epilepsy. Parasomnias, sleep disorders and narcolepsy as well as cerebral vascular imitators of epilepsy are also well described. The last section is relevant to psychological psychiatric imitators of epilepsy such as hyperventilation syndrome, psychogenic non-epileptic seizures, and panic attacks. Most chapters contain a review of the basic definitions and physiology of the respective differential diagnoses imitating epilepsy followed by the clinical characteristics and case vignettes. Some authors of this co-authored work provide a personal perspective regarding diagnosis and treatment. This book is of particular interest to any clinician working with epilepsy patients as it is to medical students on one side and general neurologists and specialised epileptologists on the other side. The fact that imitators of epilepsy are frequently encountered in non-neurological populations or patients presenting outside neurological services makes this book a useful addition to libraries of non-neurologists as well.

**P A J M Boon**