A transient dysfunction of the neuromuscular junction due to carbendazim intoxication

Carbendazim (C₉H₈N₂O₃ methyl 1-H-benzimidazol-2-yl carbamate) is widely used as an agricultural and horticultural fungicide and pesticide around the world. No hazardous effects of carbendazim on the health of humans has yet been reported. However, in animals, especially in rats, adverse effects, including testicular atrophy, infertility, ascendant paralysis, respiratory failure, and muscle cramps due to chronic carbendazim exposure have been well documented. Recently, we have treated a 60 year old female farmer who had been affected by excessive exposure to carbendazim. She was admitted to our clinic 3 days after the intoxication, which occurred when she disinfected nits with mitrosol, which contains carbendazim. She was exposed to carbendazim for 6 hours and at night, after returning from work, she slowly developed ptosis and dysphagia for especially liquid. She was admitted to the local state hospital and given atropine for 3 days because of suspicion of organophosphorus intoxication. However, her complaints persisted throughout this period. When she was admitted to our hospital, she had complained of dysphagia, and paroxysmal dyspnea.

Neurological examination disclosed only bilateral senility. Examination of pupils and extraocular, facial, and oropharyngeal muscles gave normal results. There was no weakness in any of the limb muscles and no sensory deficit was present. Physical examination showed a mild respiratory distress, especially during the expiratory phase of respiration. Cardiac auscultation, arterial blood pressure measurements, and electrocardiographic findings were all normal. Routine biochemical analysis, complete blood count, and blood acetylcholinesterase (AChE) concentration were normal. Arterial blood gases were also within normal limits.

Electrophysiological investigations were carried out on the 4th day of intoxication. Sensory and motor nerve conduction measurements did not show any abnormality. The results of needle EMG from distal and proximal muscles of the upper and lower limbs were also normal. Repetitive nerve stimulation tests (RNSTs) were carried out for the assessment of motor end plates in ala nasi and biceps brachii muscles. The RNSTs were normal at 3 and 10 Hz repetitive electrical stimulation. Voluntary single fibre EMG (SFEMG) was used to assess the orbicularis oculi muscle. Two out of five muscle fibres investigated showed increased jitter values (66 and 116 μs), with a mean value of 54 μs (fig 1).

Throughout her stay in hospital, the patient was not given any specific medication. She started to improve slowly within 15 days. Measurements of RNSTs and SFEMGs were repeated on the 19th day and the results of both tests were normal. She was discharged from hospital on the 25th day.

There are four classes of organic insecticides—organophosphates, organocarbamates, organochlorides, and pyrethroids—which are used as agricultural and animal insecticides, and they act as neurotoxins. Organophosphates are the insecticides of choice in the agricultural world and are the most common cause of poisoning among the pesticides. Organophosphates produce neuromuscular dysfunction due to irreversible binding on AChE after early and late phases of intoxication. The dysfunction in the late phase is called intermediate syndrome, which was described by Senanayake and Karalliedde. Intermediate syndrome occurs within 12–96 hours of exposure. It is a distinct clinical entity that develops after the acute cholinergic crisis (excessive acetylcholine stimulation of the muscarinic receptor) and before the expected onset of the delayed neuropathy. Respiratory symptoms are often initial features of this syndrome. Weakness of neck flexor, proximal, palmar, and extraocular muscles may be present. Spontaneous recovery usually occurs after 5 to 15 days. Atropine has no effect on intermediate syndrome because of excessive acetylcholine stimulation of the nicotinic receptor. Organophosphorus intoxication in the absence of clinical symptoms and signs has been noted after 2 years as a “jitter increasing” by single fibre EMG. The organocarbamate group, by contrast with the organophosphate group, causes reversible binding to acetylcholinesterase. The clinical presentation of organocarbamate poisoning is similar to that of organophosphates but is usually of shorter duration and lesser severity. Although agricultural organocarbamates that contain carbendazim are widely used around the world, there seem to be no reports of acute carbendazim intoxication in humans. This case is not the first acute carbendazim intoxication to be reported but also the first to demonstrate the motor end plate and neuromuscular junction dysfunction that was shown by SFEMG. In addition, this dysfunction was found to be transient, as the second SFEMG test performed on the 19th day was normal. This acute transient motor end plate dysfunction after carbendazim poisoning cannot be considered an intermediate syndrome, because the syndrome developed immediately after the exposure to carbendazim, by contrast with the intermediate syndrome of organophosphate intoxication that occurs 24 to 96 hours after the poisoning.
Refsum’s disease in an Arabian family

Refsum’s disease is a rare, autosomal recessive neurometabolic disease, characterised biochemically by accumulation of phytanic acid in blood and tissues. This is due to deficiency of the peroxisomal enzyme phytanoyl-CoA-hydroxylase (PAHX), caused by mutations of the PAHX gene on chromosome 10. As phytanic acid is exclusively of exogenous origin, patients with Refsum’s disease are treatable by a diet low in phytic acid and the phytic acid precursor. A clinical tetrad of peripheral neuropathy, retinitis pigmentosa, cerebellar syndrome, and increased CSF protein concentration was reported in most patients with Refsum’s disease.1,2

We present long term clinical and biochemical findings in an Arabian patient, finally diagnosed as having Refsum’s disease. In 1991, this 34 year old man from Egypt presented with progressive gait disorder and visual field constriction. Born in Souhag, he descended from a consanguineous union. At 19 years of age, he sustained thyphoid fever; since then he had noted hyposmia. At 31 years of age, he emigrated to Austria. Symptoms started insidiously 1 year later. Neurological examination showed bilateral sicker form restriction of temporal visual fields, wasting of leg muscles with foot drop, absence of tendon reflexes, and loss of proprioceptive sensation. Laboratory findings were normal, except for mild neutropenia (white cell count 3.2 g/l) and raised creatine phosphokinase (113 U/l). Bone marrow biopsy and immunological typing of leucocytes were normal. Tests for tuberculosis, borreliosis, brucella abortus and melenitis, leishmaniosis, HIV, herpes simples, cytoxemia, Epstein-Barr virus, syphilis, and antinuclear antibodies were all negative. Chest radiography, ECG, fundoscopy, and brain MRI were normal. Electromyography disclosed a severe sensorimotor demyelinating polyneuropathy (for example, median nerve motor conduction velocity 27 m/s). Bilaterally, short fourth toes were noted. Pathological laboratory findings (neuropenia, raised creatine phosphokinase) were unchanged; ECG, EEG, visual evoked potentials, and brain MRI were normal. Skeletal radiography showed bilateral shortening of the fourth metatarsal bones. Funduscopie and electroretinography confirmed the presence of retinitis pigmentosa. Molecular genetic testing for Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability for pressure palsies was negative. However, markedly raised phytanic acid concentrations (778 µmol/l) and occurrence of diphytanyl and monophytanyl triglycerides (8% and 36% of total triglycerides) were detected in plasma by gas and thin layer chromatography.5 Thus, on the basis of clinical and biochemical findings, the diagnosis of Refsum’s disease was established. A dietary treatment low in phytic acid and phytol, avoiding fat dairy products as well as plant fats and oils containing phytol, was given. Within a 2 year follow up neuropathy remained unchanged. Subsequently, goniarthrosis and, finally, arthritis of both shoulders became apparent. Biochemically, there was fluctuation of raised plasma phytic acid and phytanyl triglyceride concentrations.

Plasma samples for phytic acid and phytanyl triglyceride assays in the patient’s relatives became available in 1999. The family has lived in the same location in southern Egypt for several generations; the father’s mother and the mother’s grandmother were sisters. The patient has two brothers (born 1951 and 1962) and two sisters (born 1952 and 1954). The elder brother has symmetric weakness of legs starting at 28 years of age and night blindness. Neurological examination at the Cairo University Hospital in 1986 documented severe sensorimotor neuropathy with wasting and weakness of both legs. Concentration of phytic acid in plasma was increased (994 µmol/l) and diphytanyl and monophytanyl triglycerides (1% and 12% of total triglycerides) were found, substantiating a diagnosis of Refsum’s disease. Both children of the newly detected patient as well as both sisters and their children are healthy. Our patient’s younger brother seems healthy, but plasma samples were not available.

In 1998, the patient was readmitted because neuropathy had progressed (median nerve motor conduction velocity 27 m/s). Bilaterally, short fourth toes were noted. Pathological laboratory findings (neuropenia, raised creatine phosphokinase) were unchanged; ECG, EEG, visual evoked potentials, and brain MRI were normal. Skeletal radiography showed bilateral shortening of the fourth metatarsal bones. Funduscopie and electroretinography confirmed the presence of retinitis pigmentosa. Molecular genetic testing for Charcot-Marie-Tooth disease type 1A and hereditary neuropathy with liability for pressure palsies was negative. However, markedly raised phytanic acid concentrations (778 µmol/l) and occurrence of diphytanyl and monophytanyl triglycerides (8% and 36% of total triglycerides) were detected in plasma by gas and thin layer chromatography.7 Thus, on the basis of clinical and biochemical findings, the diagnosis of Refsum’s disease was established. A dietary treatment low in phytic acid and phytol, avoiding fat dairy products as well as plant fats and oils containing phytol, was given. Within a 2 year follow up neuropathy remained unchanged. Subsequently, goniarthrosis and, finally, arthritis of both shoulders became apparent. Biochemically, there was fluctuation of raised plasma phytic acid and phytanyl triglyceride concentrations.

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Our patient’s father, born 1928, has diabetes mellitus type II and mild Parkinson’s disease; his mother, born 1931, is healthy. In all these persons normal phytic acid and triglyceride values were obtained.

Refsum’s disease is predominantly found in Scandinavians and the populations originating from northern Europe, but is also seen among other ethnic groups and locations where any connection with the Vikings is unlikely.6 In Austria (8 million inhabitants), 11 patients with Refsum’s disease were detected within six families. To our knowledge, this is the first report on the occurrence of Refsum’s disease in an Arabian family from Egypt, manifesting in two brothers born from consanguineous antecedents. Thus, neurologists should be alert in diagnosing and treating Refsum’s disease in this population.

Our patient’s clinical phenotype was that of classical adult Refsum’s disease, however, without a cerebellar syndrome. Absence of cerebellar and other brain lesions was substantiated by repeatedly normal brain MRI imaging, a finding not reported hitherto in Refsum’s disease. Our findings therefore seem to question the validity of cerebellar involvement as a component of the clinical tetrad in Refsum’s disease.2,4 There is ample evidence that Refsum’s disease is an affection of the peripheral nervous system, and gait ataxia caused by loss of propriocceptive sensation may mimick cerebellar ataxia.

Skeletal abnormalities, particularly the bilateral shortening or elongation of the third and fourth metatarsal and metacarpal, are common findings in Refsum’s disease; in our patient only symmetrically short fourth metatarsal bones were present (fig 1). Obviously, the short toes were overlooked at the first presentation, because monosymtomatic neuropathy was falsely suspected. Thus, the finding of short toes in a patient with otherwise unexplained demyelinating neuropathy may prompt the clinical diagnosis of Refsum’s disease.

Recent recurrent neuropenia occurring in our patient could not be explained by common causes of neuropenia such as chronic infection, toxic drug effects, inflammatory diseases, or hypersplenia. A toxic effect of phytic acid on leukoepit bone marrow cells might be considered; however, neuropenia has not been described in Refsum’s disease hitherto. Speculatively, there might be a coincidence of idiopathic granulocytopenia and Refsum’s disease in our patient.

We are greatly indebted to our patient for permission to publish this report. Surcal nerve biopsy was kindly provided by Professor E Sluga. We thank Ms Astrid Hobel and Ms Regina Sundt for excellent technical assistance in the phytanic acid and phytanol assays. Ms Astrid Hobel and Ms Regina Sundt for excellent technical assistance in the phytanic acid and phytol assays in the patient’s father, born 1928, has diabetes mel- litus type II and mild Parkinson’s disease; his mother, born 1931, is healthy. In all these persons normal phytic acid and triglyceride values were obtained.

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A case of malignant lymphoma exhibiting leptomeningeal metastasis: Or another lymphoma associated event?

The frequency of the involvement of non-Hodgkin’s lymphoma in the CNS has been reported to be less than 10%. Moreover, as those patients have often been resistant to both chemotherapy and radiation therapy, their prognosis has been very poor. We report herein a rare case of malignant lymphoma showing bilateral homogenous and symmetric enhancement of multiple cranial nerves, with the patient’s postmortem examination providing controversial pathological findings. A 50 year old woman developed supraclavicular lymph node swelling about 1 year ago, and was diagnosed as having malignant lymphoma (non-Hodgkin’s lymphoma, diffuse large B cell type) after pathological examination of the lymph node. She then received systemic chemotherapy and peripheral blood stem cell transplantation. After six courses of CHOP therapy, she achieved complete remission and was discharged. A few weeks later, she gradually lost her appetite and her temperature remained consistently raised above 38°C for several days. One day before readmission, she noticed double vision, dysphagia, and hoarseness. Neurological examination demonstrated bilateral ptosis, dilatation of bilateral pupils being sluggishly reactive to light, paralysis of extraocular movement, and bilateral hearing disturbances. Except for the involvement of cranial nerves, no other neurological deficits were evident. Intriguingly, her cranial MRIs demonstrated marked bilateral swelling of the oculomotor nerves and trigeminal nerves, both with homogenous gadolinium (Gd) enhancement (fig 1A and B). The facial and acoustic nerves showed Gd enhancement partly in the their canals. The accessory nerves also demonstrated homogenous enhancement without definite swelling. Within the spinal cord, some of the cauda equina showed partial Gd enhancement (figure E). Cytological fluid examination disclosed pleocytosis (64/mm³) and raised protein content (586 mg/dl). Cytological examinations demonstrated class V, which were compatible with malignant lymphoma cells. On the basis of these findings, we suspected the recurrence of malignant lymphoma in the CNS system, and performed whole brain irradiation and intrathecal administration of both methotrexate (MTX) and cytosine arabinoside (Ara-c). Even after a total of 20 Gy irradiation and four courses of intrathecal chemotherapy, her clinical symptoms did not improve, and lymphoma cells still remained in the CSF. The number of cells (8/mm³) and protein content (84 mg/dl) in the CSF, however, had very much improved, repeated MRI studies could not detect any Gd enhancement in the cranial nerves, and previously recognised swelling in the oculomotor nerves and trigeminal nerves had been fully resolved. During the course of her treatments, she developed multiple organ failure, disseminated intravascular coagulation, and finally she died. Postmortem examination disclosed massive infiltration of lymphoma cells into the liver, kidney, bone marrow, and visceral lymph nodes. Lymphoma cells were recognised histologically in the dura and cauda equina, which had previously exhibited Gd enhancement in the spinal cord (fig 1E and F). Immunohistochemical examinations of that specimen indicated that these infiltrating cells were positive with L26, and were subsequently determined to be B cell lymphoma. However, despite our further extensive investigations of other parts of her CNS, no lymphoma cells could be detected, even in the cranial nerves that had shown previous Gd enhancement. Additionally, we could not detect even the smallest traces of the previous tumour infiltration including their necrosis affected by the irradiation or intrathecal chemotherapy (fig 1C). Without any infiltration of lymphoma cells, the oculomotor nerves and trigeminal nerves had markedly lost Luxol fast blue (LFB) staining and indicated a wide range of myelin damage (fig 1D). Until now, the enhancement of cranial nerves or spinal nerve roots on MRI has often been reported in inflammatory neuropathies, such as chronic inflammatory demyelinating neuropathy (CIDP). Such inflammatory demyelinating neuropathy has been described as a cause of spontaneous Gd enhancement in the CNS system. However, the aetiology of the persistent enhancement in the cranial nerves in this case is difficult to explain. The authors believe that further studies are necessary to elucidate the mechanism of Gd enhancement in this rare case.
neuropathy (CIDP). In these circumstances, abnormal enhancement may be secondary to myelin breakdown and the low degree of inflammation seen in nerve biopsies. In the present patient, no inflammatory changes, including cellular infiltrates, vasculitis, or microangiopathy, were recognized on the examined tissues and therefore the simple reviews describing MRI enhancement of multiple bilateral cranial nerves in patients with lymphoma, or detailed pathological findings regarding those damaged cranial nerves. Most of the reported cases have demonstrated direct tumour invasion (classically known as Garsin syndrome, skull base tumour invasion) and accordingly, have allowed the diagnosis of leptomeningeal involvement. Initially, we considered that she had leptomeningeal carcinomatosis because positive results of cytological examinations of the CSF may well suggest the infiltration of the lymphoma cells into the cranial nerves. However, retrospectively, the enhancement pattern of the cauda equina that contained lymphoma cells was quite different from that of cranial nerves without lymphoma cells. The former showed spotty or partial enhancement, but the latter demonstrated a homogeneous enhancement pattern accompanied by nerve swelling. These homogeneous enhancement patterns looked more like neuropathies mediated by the immunological disturbances than neuropathies influenced by direct tumour infiltration, and might be characteristic features. Although we could not necessarily exclude the possibility of direct infiltration of lymphoma cells into the cranial nerves, our results, as confirmed by pathological investigations, could indicate the existence of another mechanism associated with lymphoma causing cranial neuropathy, especially related to the loss of myelin.

The Glu298Asp polymorphism in the NOS3 gene is not associated with sporadic Alzheimer’s disease

Nitric oxide (NO) production by microglial cells, astrocytes, and brain microvessels is enhanced in patients with Alzheimer’s disease, and there is a growing evidence that NO is involved in neuronal death in Alzheimer’s disease. The of reactive oxygen caused by NO in the brain could be genetically regulated, and NO synthase (NOS) genes could modulate the susceptibility of developing the disease. Two isoforms of NOS, inducible (NOS2) and endothelial (NOS3), have been examined in Alzheimer’s disease. A pentaneucleotide repeat polymorphism within the promoter region of the NOS2 gene is not associated with Alzheimer’s disease but may be a predisposing factor in the development of dementia with Lewy bodies. Similarly, a rare polymorphism in a 27 base pair repeat in intron 4 of NOS3 is not linked to an increased risk of developing Alzheimer’s disease. On the other hand, Dahiyat et al.42 analysed a missense mutation Glu298Asp polymorphism (variant in exon 7 of the NOS3 gene in a British population sample and found an increased frequency of the Glu/Glu genotype among patients with Alzheimer’s disease compared with controls. Interaction with the APOE polymorphism in the Glu298Asp gene was also found. However, a recent American series disclosed no significant increase in the risk of Alzheimer’s disease with homozgyosity for the Glu allele in the Glu298Asp polymorphism. Thus, we investigated the association of this polymorphism and Alzheimer’s disease in a Spanish case-control study. The study included 301 patients (66% women; mean age at censoring 75.2 years (SD 9.0), range 50 to 98 years; mean age at onset 71.5 years (SD 8.9), range 40 to 95 years) who met National Institute of Neurological and Communicative Disorders and Stroke criteria for probable Alzheimer’s disease. Control subjects were 309 unrelated patients (71% women; mean age 80.3 years (SD 9.0), range 50 to 98 years) who met National Institute of Neurological and Communicative Disorders and Stroke criteria for Alzheimer’s disease. The failure to detect an association between Alzheimer’s disease and homozgyosity for the Glu allele in codon 298 of NOS3 could not be ascribed to lack of statistical power because our sample of 301 patients and 309 controls had the power to detect an OR of at least 1.7 assuming a significance level (p) of 0.05, an exposure frequency of 0.5, and an exposure frequency of 0.33 in controls (those having the Glu/Glu genotype). By comparison, the OR for the Glu/Glu genotype in the British sample was 2.04. The most likely interpretation of this discrepancy would be an ethnic difference in Alzheimer’s disease susceptibility associated with the polymorphism. In fact, it is noteworthy that the Glu allele frequency of our sample was 56% which was less than reported for the controls from the United kingdom (65%) and the United States (71%). On the other hand, the frequency of the Glu/Glu genotype in our patients with Alzheimer’s disease, which was similar to the frequency in the controls, was less than the corresponding frequencies in British and North American patients by 25% and 13%, respectively. These findings suggest that the frequency of the Glu298Asp polymorphism may vary considerably within different ethnic groups.

Table 1 Glu298Asp NOS3 genotype and allele frequencies in patients with Alzheimer’s disease (AD) and control subjects

<table>
<thead>
<tr>
<th>Genotype (n %)</th>
<th>Glu298Asp NOS3</th>
<th>Glu298Asp APOE</th>
<th>Glu298Asp APOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu/Glu</td>
<td>125 (43.4)</td>
<td>62 (50)</td>
<td>20 (16)</td>
</tr>
<tr>
<td>Glu/Asp</td>
<td>176 (57.1)</td>
<td>92 (50)</td>
<td>30 (17)</td>
</tr>
<tr>
<td>Glu/Asp</td>
<td>301 (97.3)</td>
<td>51 (37)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Glu/Asp</td>
<td>309 (100)</td>
<td>145 (47)</td>
<td>63 (20)</td>
</tr>
<tr>
<td>Control subjects:</td>
<td>125 (43)</td>
<td>62 (50)</td>
<td>20 (16)</td>
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</tbody>
</table>

*Age at onset; APOE-ε4 = no copies of ε4; APOE-ε4+ = one or two copies of ε4.

Although our data confirm the well established association between APOE ε4 and Alzheimer’s disease, our results do not support the notion that the Glu298Asp genotype
in the 298 codon of NOS3 gene is a risk factor for Alzheimer’s disease, neither through an independent effect nor through interaction with the existing APOE e4 risk.

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How well does the Oxfordshire Community Stroke Project classification predict the site and size of infarct of brain imaging?

Mead et al very justifiably draw our attention to the value of clinical assessment of patients with stroke. The cohort they describe is heterogenous—that is, patients with acute stroke and non-acute patients attending an outpatients’ clinic. Clinical features of stroke syndrome seem to predict the anatomical site and size of infarct. We presented an abstract at the 7th European Stroke Conference describing the correlation of CT features and clinical stroke syndromes on Oxfordshire Community Stroke Project classification. In a study of 202 patients with acute stroke, the clinical examination being performed within 3 days of admission to the hospital and the CT performed at a mean duration of 3.5 (SD 2.6) days. Whereas there was a very good correlation between these two measurements (r=0.71), the group with lacunar infarcts had a heterogenous presentation, only 20% of patients with a visible lacunar infarct on CT had a lacunar infarct syndrome on clinical examination, the rest having some form of cortical clinical feature—that is, dysphasia, neglect, or hemi-anopia in addition to motor, sensory, or sensorimotor deficit. Similarly a good proportion of patients with large (12%) and small cortical infarcts (24%) had only a lacunar syndrome on clinical classification.

What are the clinical implications of these findings? Should the management and investigation of patients with acute stroke depend on clinical assessment rather than on CT finding? What about the prognostic relevance of the two findings for outcome? We reported that there was a higher mortality in patients with a visible lacunar infarct compared with the clinical lacunar syndrome; the difference, however, was not significant (29% vs 11%, p=0.09).

The likely explanation is that some of these patients had cortical clinical syndromes associated with visible mortality.

Two of our recent patients admitted with partial anterior circulation infarct syndromes had evidence of only lacunar infarcts on CT. Should these patients undergo carotid investigation and how about their long term prognosis? In the study by Mead et al only 54% of the subcortical infarcts had clinical lacunar syndromes.

The lacunar infarcts thus have a heterogenous clinical presentation. Brain CT is therefore essential to determine the site and size of infarcts in all patients with acute stroke in whom further investigations are to be performed—that is, carotid scanning; the decision on whether or not to investigate carotid circulation should depend on the collective information obtained from CT and clinical examination. Similarly the prognosis of mortality, one of the concerns of patients presenting with acute stroke, should also be made on the information obtained on both these measures, the CT and clinical symptomes being complementary to each other.

In the absence of a visible infarct on CT, the decision on management and prognosis depends on clinical assessment alone. The absence of a visible infarct is usually associated with a better outcome but may indicate the need for carotid scanning if there are any clinical features of cortical involvement. Patients with lacunar infarcts with clinical cortical features do not as well as patients with lacunar infarcts without cortical features. The explanation for cortical features in lacunar infarcts is not clear but may be due to a variation in circulation in these patients.

The authors reply:

Sharma et al raise some interesting points concerning the relation between the clinical classification of stroke and the site size of infarcts on brain imaging. Firstly, they point out that patients with a lacunar infarct on brain imaging may present with cortical symptoms. One likely explanation for this apparent anomaly is that the lacunar infarct was old, and that the new cortical infarct responsible for cortical symptoms had not become visible on CT. Secondly, they raise the issue of whether the investigation and management of patients with acute ischaemic stroke should depend on clinical assessment or on CT findings. In acute ischaemic stroke, not all infarcts are visible on CT and, in these patients, clinical classification must be relied on. However, if subsequent brain imaging demonstrates a new infarct in the “wrong” place, then the clinical classification could be modified according to CT. For example, if a patient presents with a pure motor stroke (clinically a lacunar syndrome) but has a recent cortical infarct on CT, then this patient is more likely to have carotid or cardiac disease than a patient with a pure motor stroke who has a lacunar infarct on CT.

Thirdly, Sharma et al suggest that because lacunar infarcts present in a heterogeneous way, CT is essential to determine the site and size of infarct. We would agree that a CT is essential in patients presenting with acute stroke, but the main reason is to distinguish haemorrhagic from ischaemic strokes. So many patients with a lacunar syndrome have either normal CT, or several candidate lesions, that it is certainly not possible to identify a relevant lesion in every case.

Fourthly, they suggest that the decision on whether or not to investigate the carotid circulation should depend on the collective information obtained from CT and the clinical examination. We suggest that patients should be investigated for carotid disease if they have experienced a recent (<6 months) carotid territory minor non-disabling ischaemic stroke or transient ischaemic attack and would be medically fit (and willing) to undergo surgery (they fulfill criteria of symptomatic carotid surgery trials). In centres where access to carotid Doppler imaging is limited, it is particularly important that imaging should be performed only in patients who fulfill these criteria. Of course, it is still unclear whether severe ipsilateral carotid disease is present in patients with lacunar stroke, causative or coincidental, and whether endarterectomy in patients with lacunar ischaemic events will confer as much benefit as it does for those with cortical events. Further analyses of individual patient data from the symptomatic carotid surgery trials will help resolve this dilemma.