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Leukoencephalopathy associated with khat misuse

The leaves of the tree *Catha edulis*, or khat (also qat and kat) are chewed by a large proportion of the adult population of the Yemen, and throughout Saharan and sub-Saharan Africa. The leaves are also chewed by members of the Yemeni and Somali community in the United Kingdom.[1] The psychoactive constituents of khat are cathin (*d*-norisoephedrine), cathidine, and cathinone (an alkaloid with a structure resembling ephedrine and amphetamine) and users report a mild euphoria similar to that of amphetamine.[1] Khat is acknowledged as a precipitant of psychosis and has also been reported to cause cognitive impairment.[2] We report a case in which khat chewing has been associated with a severe and disabling neurological illness.

A 56 year old Somali living in the United Kingdom for the past 18 years was admitted to a psychiatric hospital with a 5 week history of progressive confusion and agitation. His family reported that he had been chewing khat, in their opinion to excess, every day during that time but had stopped 2 days before admission. There was one previous admission to hospital 9 months previously with khat induced psychosis, from which he recovered without complications within 24 hours. On this occasion, shortly after admission, his conscious level deteriorated abruptly and he was referred for neurological opinion. He was apyrexial and general medical examination was normal. He opened his eyes spontaneously but there was no verbal response and he did not obey commands. He withdrew all four limbs to pain. Upper and lower limbs were held in flexion with markedly increased tone. Reflexes were brisk but equal. The right plantar was extensor. There were bilateral palmomental and grasp reflexes.

Full blood count, urea and electrolytes, glucose, liver function tests, thyroid function test, viral serology, and malaria screen all gave normal results. Tests for HIV antibody, serum angiotensin converting enzyme, white cell enzymes, and serum and urinary porphyrins were negative. Erythrocyte sedimentation rate on admission was 58 mm/h.

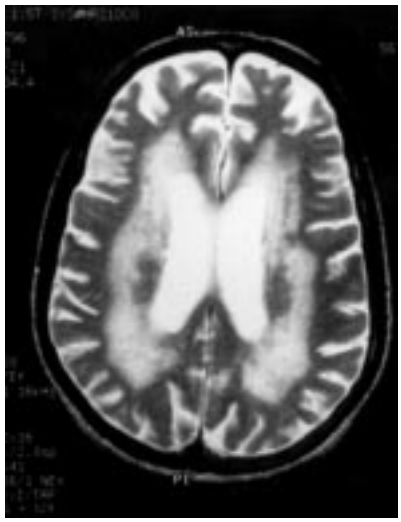
Examination of the CSF showed normal opening pressure, protein 0.27 g/l, glucose 4.3 mmol/l (blood glucose 6.1 mmol/l), and no cells. His initial EEG was abnormal with diffuse slow waves indicative of widespread cerebral dysfunction.

A chest radiograph and ultrasound examination of the abdomen were normal. Cranial MRI, although contaminated by movement artefact, showed diffuse abnormality in the deep cerebral white matter of both cerebral hemispheres. Fourteen days after admission he was witnessed to have a single brief adversive seizure with eye and head deviation to the right.

The patient was admitted to a rehabilitation unit. His mini mental state examination score and Barthel scores were zero. Feeding by percutaneous gastrostomy was started. A trial of intravenous methylprednisolone (1 g on 3 consecutive days) gave no benefit. Repeated EEGs (on four occasions) showed diffuse slow waves only. A second MRI (figure) 3 months after onset of symptom showed the presence of a continuing diffuse extensive abnormal signal in the deep white matter of both cerebral hemispheres with marked cortical atrophy. Brain biopsy (via right frontal craniotomy) was performed 3 months after the onset of his illness. There was no evidence of acute inflammation, vasculitis, or infarction.

While undergoing rehabilitation there has been slow improvement in his cognitive and locomotor function. After 1 year he is able to open and close his eyes, occasionally verbalise, localise pain, and obey simple commands. His plantars are flexor but he has persistent grasp and palmomental reflexes. His nutrition is maintained by gastrostomy and he has an indwelling catheter.

The clinical presentation, EEG, and MRI findings suggest a rapidly progressive leukoencephalopathy. There are no previous reports of leukoencephalopathy in association with khat or amphetamine misuse; it has, however, been reported in association with other recreational drugs taken by mouth or inhalation.[3 4] An alternative for this man's presentation is a necrotising vasculitis, a well described complication of oral amphetamine misuse.[5] The clinical features, MRI appearance, brain biopsy, absence of haemorrhage, and lack of response to steroids make this unlikely.



Cranial MRI 3 months after onset of symptoms showing diffuse signal abnormality in the deep white matter of both cerebral hemispheres. There is also marked cortical atrophy.

The likely precipitant of this man's illness seems to be his use of khat. A drug screen on admission was negative, and his family denied misuse of other drugs. It remains possible that the sample of khat chewed by this man was contaminated. We are unaware of any previous reports of khat misuse with severe neurological deterioration; previous cases may not have been investigated or reported. In reporting this case our intention is to alert others to a possible complication of the misuse of this drug. Evidence of other cases would provide a powerful argument for the restriction of import and sale of khat.

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Necrotising vasculitis with conduction block in mononeuropathy multiplex with cold agglutinins

Cold agglutinins are cold reactive autoantibodies that have haemolytic effects on red blood cells mediated via complement fixation. Neuropathy associated with cold agglutinins has been described,[1–5] however, details of its pathomechanism are unclear. Here, we report the clinical, electrophysiological, and pathological findings of a mononeuropathy multiplex in a patient with cold agglutinins, who responded very well to plasmapheresis.

A 72 year old man was admitted with a 1 month history of progressing dysaesthesia and weakness of the limbs. He had no anaemia, jaundice, hepatosplenomegaly, or lymphadenopathy. Cranial nerves and the cerebellum were not involved. There was severe weakness and atrophy of bilateral thenar, interossei, and plantar muscles with severe dysaesthesia of both palms and plantaris. Pin prick and light touch were reduced as well as position and vibratory sensation in both hands and feet. Deep tendon reflexes were hypoactive. Babinski's sign was negative.

Laboratory investigation showed a raised erythrocyte sedimentation rate: 52 mm/hour (normal <10) and serum C reactive protein: 1.8 mg/dl (normal; < 0.5). Blood cell counts were within normal limits. The following were normal or negative; IgG, IgA, IgE, IgM,

M-protein, direct and indirect Coombs tests, cryoglobulin, antibodies to mycoplasma, myelin associated glycoprotein, gangliosides (GM1, GD1b, asialo-GM1, GT1b, GQ1b, Gal-C), P-ANCA, and C-ANCA. The CSF was normal. Titre of cold agglutinins was detectable at 1:1024 at 4°C (normal; <1:256). The patient's serum agglutinated adult group OI-red blood cells, but not Oi-red blood cells or human cord red blood cells, signifying cold agglutinins with I specificity. Immunoelectrophoresis of the eluate confirmed IgM composition.

The initial nerve conduction study showed severe diminution or absence of compound muscle action potentials (CMAPs) with mildly diminished conduction velocities. F wave latencies were mildly prolonged. There were no evoked sensory nerve action potentials (SNAPs) in median, ulnar, and sural nerves bilaterally. Electromyographic studies of the affected muscles showed moderate neurogenic changes, but there were no fibrillation potentials except in the left anterior tibialis muscle. Sural nerve biopsy was performed. Epineurial vessels were surrounded by mononuclear cell infiltrates (figure A). Some vessels had focal necrosis of their wall. The small vessels in the endoneurium and epineurium showed slugging of red blood cells. The densities of large and small myelinated fibres were markedly decreased (diameter<5 μm: 1504/mm^2, diameter >5 μm:708/mm^2, total: 2212/mm^2)(figure B). Teased fibre analysis showed that 90% of the fibres were undergoing axonal degeneration.

Oral prednisolone (30–50 mg/day) for 4 weeks reduced the erythrocyte sedimentation rate and C reactive protein, but not the serum titre of cold agglutinins; neither was there any improvement of symptoms. He received massive dose intravenous corticosteroid therapy. This moderately improved the muscle strength and sensory disturbance. Follow up nerve conduction studies (71 days after the initial study) suggested conduction block of the right median nerve on the forearm (CMAP, duration at the wrist: 2.76 mV, 8.4 ms; CMAP, duration at the elbow: 1.87 mV, 8.8 ms), whereas CMAP could not be elicited in the initial study. We adapted the following criteria to define conduction block: <15% change in duration and >20% fall in negative peak amplitude between proximal and distal sites by percutaneous supramaximal stimulation of motor nerves. As the conduction block might delay smooth recovery of symptoms, Double filtration plasmapheresis was performed four times. After the second plasmapheresis, dysaesthesia and muscle strength improved remarkably.The titre of cold agglutinins was reduced to 1:64. The motor nerve conduction velocity (MCV) of the right median nerve likewise improved (pretreatment; 40.0 m/s, posttreatment; 57.0 m/s). Double filtration plasmapheresis was followed by oral azathioprine (50 mg/day) with tapering of steroid. He was discharged on prednisolone (20 mg/day). In the subsequent 4 years, he has had mild exacerbation of dysaesthesia that responded to intermittent steroid therapy.

Characteristic features of the present case are as follows: (1) subacute onset of mononeuropathy multiplex; (2) necrotising vasculitis with marked loss of myelinated fibres; (3) probable conduction block in the median nerve; (4) increased concentrations of serum titres of cold agglutinin; and (5) marked response to plasmapheresis. Extensive investigation for other causes of neuropathy was negative except for an increased serum concentration of cold agglutinins, which strongly suggests that cold agglutinins may play an important part in the induction of neuropathy in this case.

Six patients with neuropathy associated with cold agglutinins have been reported[1–5] including our patient. Cold agglutinins are cold reactive autoantibodies that react with the antigenic determinant termed I/i or Pr present on glycoproteins and glycolipids in erythrocyte membranes. Arai *et al*[1] reported a case of polyneuropathy and IgMκ M proteinemia with anti-Pr2 CA activity. IgM M protein cross reacted with sialosyl paragloboside, GT1b, GD1a, GD1b, GM3, and GD3 present in myelin and in endothelial cells of the peripheral nervous system. It has been speculated that anti-Pr2 IgM protein induced immune mediated damage to vascular endothelium and peripheral nervous system myelin. A similar pathomechanism has been postulated in the other cases.[2–3] However, necrotising vasculitis has never been reported in neuropathy with cold agglutinins. This is the first demonstration of vasculitic neuropathy with cold agglutinins. Although the mechanism for neuropathy with cold agglutinins is unknown, mechanisms similar to those in cryoglobulinaemic neuropathy have been postulated.[4] The hypotheses are (1) immunologically mediated demyelination; (2) ischaemic injury secondary to slugging or agglutination of red blood cells in the vasa nervorum; and (3) an associated vasculitis. In the present case, we have confirmed the necrotising vasculitis and probable conduction block. Pathophysiological explanations for association of vasculitis and conduction block may be as follows. Firstly, conduction block may occur as a consequence of nerve ischaemia due to small vessel occlusion. There have been reports of conduction block occurring in vasculitic neuropathy which support this possibility. Secondly, humoral factors including cold agglutinins may induce immune mediated demyelination in the peripheral nervous system. Taken together, neuropathy with cold agglutinins may involve immunologically mediated demyelination, microcirculation occlusion, and vasa nervorum vasculitis. The diversity of pathomechanisms may come from the difference target antigens recognised by cold agglutinins. Plasmapheresis proved effective in all cases. These findings strongly suggest that humoral factors including cold agglutinins may play an important part in the induction of neuropathy with cold agglutinins. We recommend plasmapheresis as first choice treatment for neuropathy associated with cold agglutinins.

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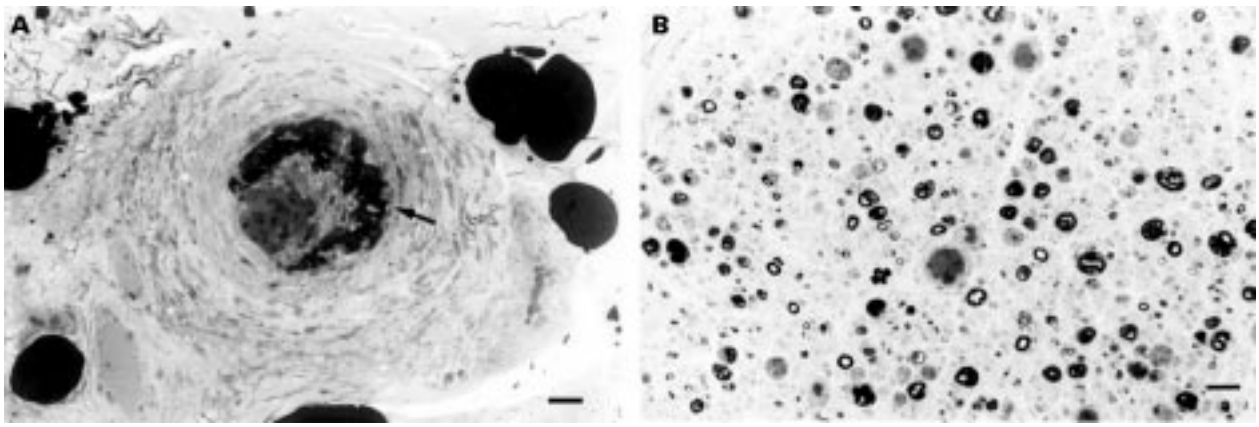

(A) Sural nerve (toluidine blue staining) showing epineurial vessel surrounded by mononuclear cell infiltrates. Note fibrin deposition (arrow) and necrosis in media. (bar=20 μm). (B) Most of myelinated fibres are undergoing axonal degeneration. Many macrophages containing myelin debris infiltrate the endoneurium. (bar=30 μm).

CORRESPONDENCE

The cholinergic hypothesis of Alzheimer's disease: a review of progress

I read with interest the review of Francis *et al* regarding the progress of the cholinergic hypothesis of Alzheimer's disease.[1] They mentioned that donepezil produced improvement or no deterioration in more than 80% of patients, and that such responses should be viewed positively considering the progressive, degenerative nature of the disease. Various donepezil manufacturer's medical representatives presenting data from a clinical study[2] also commonly use this statement. However, this only partially reveals the truth. In fact, the same study produced improvement or no deterioration in 59% patients on placebo. I think that the beneficial effect of donepezil in particular clinical trials should always be critically reviewed in comparison with placebo. In addition, as both 24 week placebo controlled donepezil trials performed so far excluded patients with behavioural disturbances, my impression is that the positive effect of donepezil on the symptoms of behavioural disturbances still remains controversial. In fact there are reports that donepezil might induce behavioural disturbances in patients with Alzheimer's disease.[3 4] Therefore I would be extremely cautious about prescribing donepezil to patients with Alzheimer' s disease accompanied by behavioural disturbances.

Finally, donepezil was never investigated in a 30 week randomised double blind study as was mentioned in the review. The authors are probably referring to the randomised 24 week double blind placebo controlled trial with an additional 6 week single blinded placebo phase.

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The authors reply:

We thank Professor Babic for the letter, which raises several interesting points. We agree that it may be more helpful to put the results attributed to treatment with donepezil in the context of the placebo response. In general, looking at this as a class effect in relation to several compounds, the picture emerging is that about twice as many people obtain a response to active treatment as to that with placebo. The high placebo response is a common factor in most studies in this field and is worthy of some explanation in its own right. Although it seems that these studies compare drug treatment with that of a placebo (one treatment against no treatment), the reality is that it is a comparison of patients receiving two treatments against other patients who are receiving one form of treatment. The additional treatment regime is, of course, the care and attention that they receive by being part of the clinical study, which often seems to have an impact, not just on the patient but also on their main carer or carers.

As far as behavioural disturbances are concerned, however, our review was making the point that evidence is emerging from clinical trials to suggest that cholinomimetic drugs as a whole may have a beneficial effect on some non-cognitive behavioural symptoms. This has now been reported for at least two cholinesterase inhibitors, and two muscarinic agonists.[1–5] In particular, a clear link is emerging between psychotic symptoms and cholinergic dysfunction. Thus, Bodick *et al*[2] have shown that the M_1/M_4 agonist xanomeline causes a dose dependent reduction in hallucinations, agitation, and delusions in a 6 month randomised double blind placebo controlled, parallel group trial. In addition, Cummings and Kaufer[6] have shown that the cholinesterase inhibitor tacrine is more effective in reducing psychotic features than cognitive disturbances; tacrine also reduces or abolishes hallucinations in Parkinson's disease.[7] Another cholinesterase inhibitor, metrifonate, was also shown to reduce the number of hallucinations in a 26 week randomised, double blind, placebo controlled safety and efficacy study in patients with Alzheimer's disease. Further support for a link between acetylcholine and psychosis derives from postmortem data showing that the activity of choline acetyltransferase in the temporal cortex of patients with Lewy body dementia was lower in those patients with hallucinations than in patients without this feature.[8] Finally, in animals the partial M_2/M_4 agonist (5R,6R)6-(3-propylthio-1,2,5-thiadiazol-4-yl)-1-azabicyclo[3.2.1]octane produced a preclinical profile suggestive of antipsychotic efficacy[9] and that the psychomimetic NMDA receptor antagonist ketamine (when administered at subanaesthetic doses) reduced brain concentrations of acetylcholine.[10] Thus, on the basis of both clinical and preclinical data, a clear rationale is emerging for prescribing cholinomimetic agents for treating the non-cognitive behavioural symptoms associated with dementia, particularly psychosis.

Professor Babic is also correct in identifying two of the studies referred to as the 30 week randomised multicentre placebo controlled parallel group studies, which included a 24 week double blinded treatment phase.

We are grateful to your correspondent for providing us with the opportunity to clarify these points.

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BOOK REVIEWS

Clinical Management of Diabetic Neuropathy. Edited by ARISTIDIS VEVES. (Pp 348, US$125). Published by The Humana Press, New Jersey, 1998. ISBN 0-896-03528-X.

The neuropathies of diabetes are common (as the chapters in this book repeatedly remind us) and can be very disagreeable. Symptomless neuropathy underlies foot ulceration and sepsis as the commonest clinical consequence of diabetic neuropathy but other extremely unpleasant disorders range from exceptionally severe pain to the whole range of problems resulting from autonomic failure. This book comprehensively covers every aspect of the subject, systematically (and at times exhaustively) from its epidemiology and pathogenesis (exhaustingly) to structural, functional, and clinical problems and their treatment. Most of the authors are well known in the field and their accounts are up to date and authoritiative.

Unfortunately, struggle as they might, all authorities have difficulty in defining what they mean by diabetic neuropathy and, in this regard, understanding of this complication both in clinical and pathological terms, as well as with regard to treatment, lags far behind that of the other classic diabetic complications, nephropathy and retinopathy. Even its classification presents problems and attempts to do so are found in four different chapters, describing four classifications. Repetition is an unfortunate feature of this book and—quite apart from the confusion over classification—aspects of pathogenesis, structural changes, epidemiology, diagrams, and some reference to treatment (for example, that of pain) appear repeatedly in different chapters in greater or lesser detail.