

LETTERS TO THE EDITOR

Death after ecstasy ingestion: neuropathological findings

Ecstasy (3,4-methylenedioxyamphetamine; MDMA) is a widely used recreational drug that has recently been associated with a syndrome of hyperpyrexia, restlessness, rhabdomyolysis, and acute renal and hepatic failure and at least nine deaths have been reported in the United Kingdom.¹ There are no neuropathological reports of patients who died after taking ecstasy.

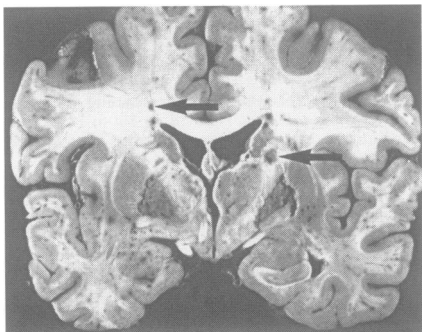
A 30 year old man attended a "rave" party where he took ecstasy, heroin, and amphetamine. The next day he drank large amounts of alcohol and was found unconscious in a pool of vomit some hours later. He had a convulsion and was admitted to hospital. He was pyrexial (38.5°C), and remained so until his death five weeks later. Creatine kinase was 11 178 IU/l (normal < 300 IU/l) on admission and 3468 IU/l four days later. He remained comatose and had no hypertonia, but had occasional generalised muscle spasms. A chest infection was treated with antibiotics. No evidence of hepatic or renal failure or diffuse intravascular coagulopathy was found. Brain CT showed clearly defined low densities in the globus pallidus bilaterally.

Postmortem examination showed bronchopneumonia, lung abscess, and pulmonary embolism. The brain weighed 1450 g after fixation. Coronal slices showed clearly demarcated bilateral necrosis of the globus pallidus (figure). There were small foci of necrosis in the white matter.

Histological examination confirmed necrosis of the globus pallidus. There was intimal proliferation in large blood vessels without necrosis or inflammation. The substantia nigra was gliotic. There was mild astrocytic gliosis in the amygdala and hypothalamus.

The cerebral white matter showed diffuse gliosis and spongy change without myelin debris or inflammation and sparing only the subcortical zones. Well defined foci of necrosis up to 0.5 cm in diameter were identified. The cerebral cortex, hippocampus, brainstem, and cerebellum were normal.

A major problem in understanding the



Coronal slice of the fixed brain showing necrosis of the globus pallidus bilaterally and foci of white matter necrosis (arrows).

pathology of this case is that, like most drug abusers, the patient took a combination of drugs. Consumption of alcohol may have potentiated their effects. The most striking neuropathological change was necrosis of the globus pallidus, an area rich in serotonergic and dopaminergic nerve terminals. Pallidal blood vessels showed changes compatible with prolonged vasospasm, possibly the result of local release of serotonin and other biogenic amines induced by ecstasy or amphetamine. Blood vessel changes have been noted after cocaine and amphetamine abuse.² The pathology resembles that of carbon monoxide toxicity, but similar white matter changes are described in nine cases of heroin abuse.³ Damage to the globus pallidus is found in hypoxic-ischaemic cerebral injury but almost always in association with damage to the hippocampus or other areas of the cerebral cortex.

Although at least nine deaths after ingestion of ecstasy have been reported,¹ neuropathological findings have not previously been described. It is important that these cases be fully studied if we are to improve our understanding of the effects of these drugs on the human brain.

M V SQUIER

Department of Neuropathology,
Radcliffe Infirmary,
Oxford OX2 6HE, UK

S JALLOH

Department of Pathology
D HILTON-JONES

Department of Neurology,
Milton Keynes General Hospital

H SERIES

Department of Clinical Pharmacology,
Radcliffe Infirmary,
Oxford OX2 6HE, UK

Correspondence to: Dr M V Squier.

- O'Connor B. Hazards associated with the recreational drug "ecstasy". *Br J Hosp Med* 1994;52:507-14.
- Klonoff DC, Andrews BT, Obana WG. Stroke associated with cocaine use. *Arch Neurol* 1989;46:989-93.
- Wolters ECh, Stam FC, Lousberg RJ, Van Wijngaarden GK, Rengelink H, Schipper MEI, Verbeeten B. Leucoencephalopathy after inhaling "heroin" pyrolysate. *Lancet* 1982;ii:1233-237.

Lewy body dysphagia

Swallowing disorders are encountered with increasing frequency in elderly people.¹ Swallowing depends on the complex interplay of sensory pathways from the tongue, mouth, pharynx, and larynx (cranial nerves V, VII, IX, X) with coordinated autonomic, voluntary, and reflex contractions involving cranial nerves V, VII, X, XI, and XII. It is therefore not surprising that dysphagia complicates a variety of neurological disorders, many of which are more common in the elderly population, such as pseudobulbar palsy due to cerebrovascular disease.¹ It is, however, seldom the sole presenting feature of neurological disorders.¹

We describe two patients with isolated painless progressive dysphagia who at neuropathological examination showed severe neuronal loss, Lewy bodies, and dystrophic neurites in the dorsal vagal nuclei, with only a few Lewy bodies in the substantia nigra, nucleus basalis of Meynert, and cerebral cortex. These patients represent a new presentation of Lewy body-associated disease.

Patient 1 was an 80 year old retired man who developed painless progressive dysphagia for solids, and to a lesser extent liquids, over a two month period. He described difficulty initiating the swallow, with regurgitation of food (solids more than liquids) from the upper oesophagus or pharynx. He lost 6 kg in weight over this period. His appetite was normal and there was no vomiting or haematemesis. Five years earlier a peptic ulcer had been diagnosed at endoscopy and successfully treated with ranitidine. Two years earlier he developed a mild left oculomotor nerve palsy of unknown cause. He took senna and fybogel for constipation, propranolol (40 mg twice daily) for long-standing paroxysmal supraventricular tachycardia, and temazepam as a hypnotic.

Examination was unremarkable except for the presence of a partial left oculomotor palsy. In particular there was no evidence of Parkinson's disease or cognitive impairment.

Endoscopic examination showed no abnormality in the stomach or oesophagus. A limited barium swallow showed the oesophagus to be slightly dilated with a minor hold up of barium at the oesophago-gastric junction. Computed tomography of the chest was normal.

He developed fatal bronchopneumonia while in hospital.

Patient 2 was an 88 year old woman who developed painless progressive dysphagia for solids more than liquids over three months. After swallowing, food was immediately regurgitated from the pharynx or oesophagus. There was no regurgitation after the meal was completed. Appetite was normal and she had no nausea or vomiting. She had lost 12 kg in weight over the preceding three months. One month before the onset of dysphagia, she had suddenly developed mild pyramidal weakness of the left arm, which was diagnosed as a stroke. She was otherwise well, took no medication, and lived an independent life.

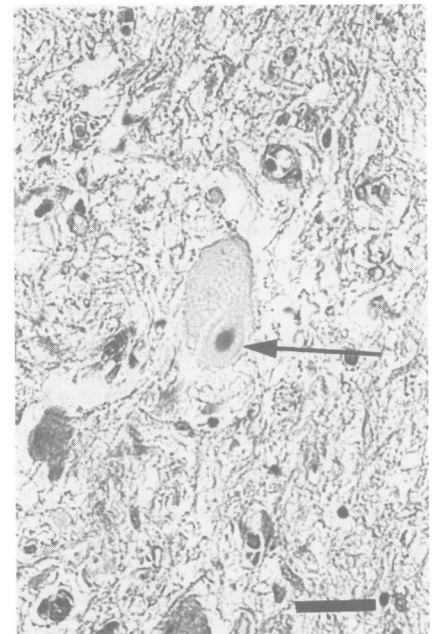


Figure 1 Swollen cell in dorsal vagal nucleus from patient 2 showing Lewy body (haematoxylin and eosin). Bar = 100 µm.

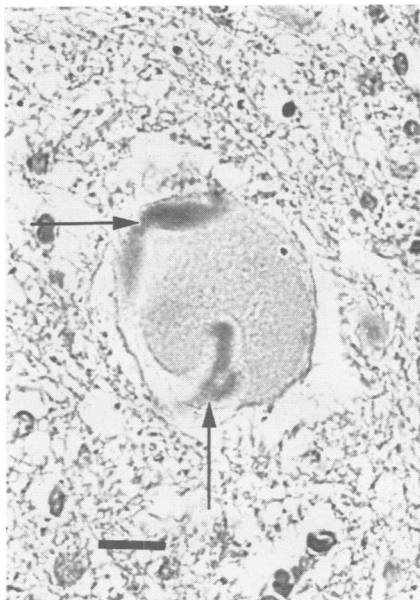


Figure 2 Swollen cell in dorsal vagal nucleus from patient 2 showing Lewy like serpiginous eosinophilic inclusions (haematoxylin and eosin). Bar = 200 μ m.

General examination showed a frail woman with mild aortic sclerosis. She had mild pyramidal weakness affecting the left arm, but neurological examination was otherwise normal, with no evidence of Parkinson's disease or cognitive impairment.

A barium swallow examination showed no obstructing lesion in the oesophagus but a paucity of peristalsis, and some tertiary contractions compatible with her age.

She died from bronchopneumonia while in hospital.

In both brains there was severe neuronal loss with ubiquitin immunoreactive dystrophic neurites and Lewy bodies in both dorsal vagal nuclei (figs 1–4). Scanty Lewy bodies, without appreciable cell loss, were detected in the substantia nigra, nucleus basalis of Meynert, and the cerebral cortex. There was no pathology in the hypoglossal

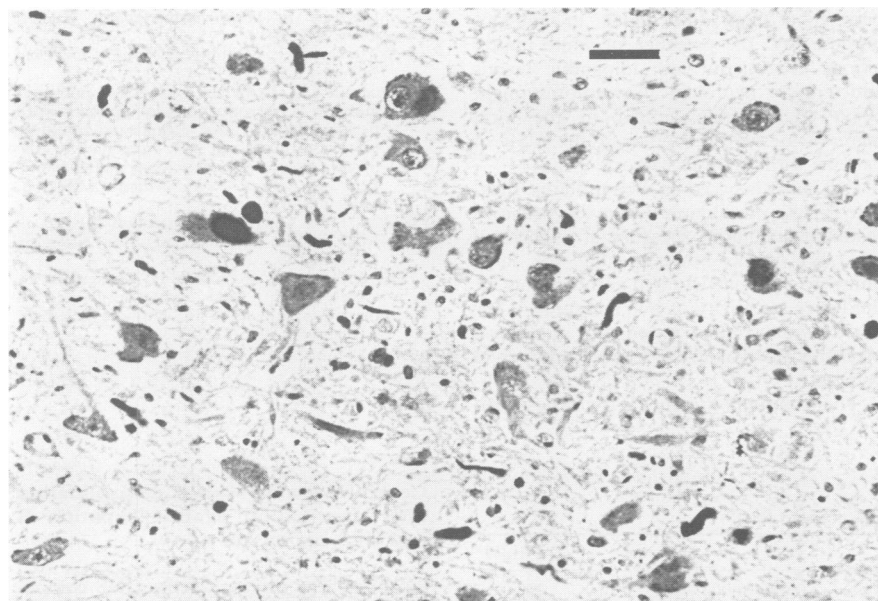


Figure 3 Abundant ubiquitin-immunoreactive neurites in dorsal vagal nucleus from patient 1 (antiubiquitin haematoxylin). Bar = 40 μ m.

nuclei and nuclei ambiguus. This dorsal vagal nuclear pathology has been described in idiopathic Parkinson's disease and diffuse Lewy body disease.³

No neuropathological basis for the partial oculomotor palsy in patient 1 was found. A small infarct in the right, posterior internal capsule was found in patient 2.

Lewy bodies are spherical, eosinophilic, ubiquitin immunoreactive neuronal inclusions.² They are found particularly in monoaminergic and cholinergic neurons of the brainstem, diencephalon, basal forebrain, and cerebral cortex.² Kosaka and colleagues were the first to draw attention to the possibility that neurodegenerative diseases associated with Lewy bodies can be considered to form a disease range based on the number and distribution of Lewy bodies.³ At one end of the range they placed patients with Lewy bodies apparently confined to the substantia nigra causing idiopathic Parkinson's disease. At the other end are patients with many and widespread Lewy bodies, including Lewy bodies in the cortex associated with a parkinsonian dementia syndrome referred to as diffuse Lewy body disease or Lewy body dementia.² Both of our patients showed severe neuronal loss from the dorsal vagal nucleus, with Lewy bodies in many remaining neurons, and dystrophic neurites. Elsewhere, scanty Lewy bodies, without significant neuronal loss were found in the substantia nigra, nucleus basalis of Meynert, and cerebral cortex. Whereas Lewy bodies, neuronal loss, and dystrophic neurites in the dorsal vagal nucleus are well described in idiopathic Parkinson's disease and diffuse Lewy body disease, they have not previously been described as the principal neuropathological finding in the absence of clinical dementia or parkinsonism.²

The dorsal vagal nucleus provides pre-ganglionic parasympathetic innervation to the oesophagus, as well as other thoracic and abdominal viscera. Although there are no reports of idiopathic Parkinson's disease presenting with isolated dysphagia, this symptom is nevertheless a common feature in both idiopathic Parkinson's disease and diffuse Lewy body disease, and patients

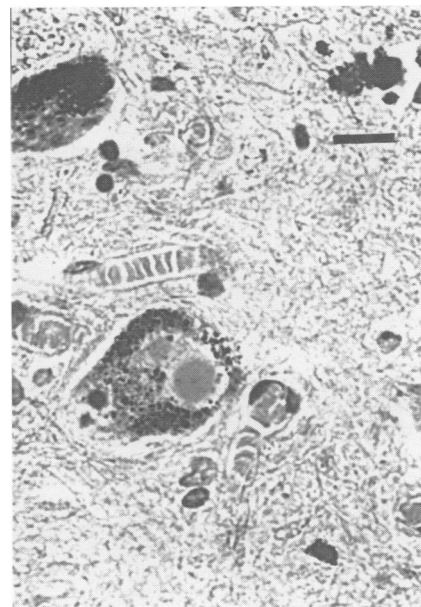


Figure 4 Classic Lewy bodies in nigral neuron, patient 1 (haematoxylin and eosin). Bar = 50 μ m.

with idiopathic Parkinson's disease complain of dysphagia far more often than do age matched subjects.⁴ There is a general correlation between the severity of swallowing dysfunction and the severity of the Parkinson's disease. In idiopathic Parkinson's disease, dysphagia is most commonly clinically localised to the oropharynx, and solids cause greater difficulty than liquids.⁵ A variety of motor abnormalities in the oesophagus have, however, been described in Parkinson's disease, including dysmotility, dilatation and pseudodiverticula.⁵ A recent study by Edwards and colleagues has shown that patients with idiopathic Parkinson's disease do not have any single characteristic video-oesophagographic abnormality.⁵

Several possible explanations have been put forward in the pathogenesis of these problems including degeneration of the dorsal vagal nucleus, peripheral dopamine depletion, Lewy body formation in the myenteric plexus, and disordered neuromuscular junction transmission.⁵

Lewy body associated diseases can therefore present as idiopathic Parkinson's disease, a parkinsonian dementia, isolated dementia, and now dysphagia.² In these patients we speculate that had pneumonia not developed, they would probably have developed idiopathic Parkinson's disease as the nigral involvement became more severe.

MATTHEW JACKSON
GRAHAM LENNOX
Department of Neurology
MARGARET BALSITIS
JAMES LOWE

Department of Pathology,
University Hospital,
Queen's Medical Centre,
Clifton Boulevard, Nottingham NG7 2UH, UK

Correspondence to: Dr James Lowe, Department of Pathology, University Hospital, Queen's Medical Centre, Clifton Boulevard, Nottingham NG7 2UH, UK.

1 Wald A. Understanding the pathophysiology of dysphagia and constipation in neurologic disorders. *Am J Gastroenterol* 1994;89:1–3.

2 Lowe J. Lewy bodies. In: Caine DB ed. *Neurodegeneration*. Philadelphia: WB Saunders and Co, 1994:51–69.

- 3 Kosaka K, Matsushita M, Oyanagi S, Mehraein P. A clinicopathological study of the "Lewy body disease". *Psychiatria et Neurologia Japonica* 1980;82:292-311.
- 4 Edwards LL, Pfeiffer RQ, Quigley EMM, et al. Gastrointestinal symptoms in Parkinson's disease. *Mov Disord* 1991;6:151-6.
- 5 Edwards LL, Quigley EMM, Harned RK, Hofman R, Pfeiffer RF. Characterisation of swallowing and defecation in Parkinson's disease. *Am J Gastroenterol* 1994;89:1525.

Local IgG production in aqueous humour in patients with idiopathic uveitis compared with MRI findings

We have previously reported an increased concentration of antibody to measles in the aqueous humour of patients with multiple sclerosis related uveitis.¹ We further found a high frequency of asymptomatic multiple sclerosis-like lesions on MRI of the brain of patients with idiopathic uveitis.² There was a significant association between MRI lesions and high aqueous humour and blood concentrations of antimeasles antibodies.³

The local production of oligoclonal IgG in the CNF has long been considered as a pathognomonic characteristic of multiple sclerosis, and also a good biological aid to its diagnosis.⁴ Oligoclonal production of IgG has also been suspected in the aqueous humour of patients with multiple sclerosis, on the basis of the ratio between albumin and IgG contents in both aqueous humour and serum.⁵

This study was aimed at determining if the presence of white matter MRI lesions in patients with uveitis was linked to an increased content of IgG in the aqueous humour, and if this increase could be explained by the high concentration of antimeasles antibodies in the aqueous humour.

Sixty eight patients with idiopathic uveitis (23 males, 45 females, aged 15-49), all free of neurological symptoms, diabetes, and blood pressure problems, were submitted to both a brain MRI examination and a sampling of blood and aqueous humour. All patients gave informed consent to their participation in this study.

The presence of white matter lesions on MRI was determined in each patient by three independent radiologists according to Paty's multiple sclerosis diagnosis scale.⁶

Samples of aqueous humour and blood were assayed for albumin and total IgG by laser nephelometry and measles virus, herpes simplex virus (HSV), varicella zoster virus (VZV), and cytomegalovirus (CMV) specific IgG by enzyme linked immunosorbent assay (ELISA). The following coefficients were calculated⁷: albumin quotient = aqueous humour albumin/serum albumin; IgG quotient = aqueous humour IgG/serum

IgG; IgG index = IgG quotient/albumin quotient.

The values of these three coefficients as well as optical densities in aqueous humour for each of the four virus assays were compared in patients with lesions on MRI (MRI+) and those without (MRI-) by Wilcoxon's test. Partial Spearman correlations were calculated to assess if the relation between the local IgG production coefficients and MRI was related to a specific viral expression.

The results showed an association between the presence of brain lesions and high ocular IgG production as represented by the IgG quotient ($P = 0.002$; table). Albumin quotient did not differ significantly between the groups and the association was due to differences in the values of the IgG quotient ($P < 0.05$).

Moreover the measles optical density in aqueous humour of MRI+ patients was significantly higher than that of MRI- patients. ($P < 0.0001$). We did not find a difference in VZV, HSV, or CMV optical densities between the groups. The values of the measles optical density in aqueous humour were significantly correlated with both IgG quotient ($P < 0.01$) and IgG index ($P = 0.04$). Finally, when adjusting for the effect of measles optical density in aqueous humour, the partial correlation between IgG index and MRI remained significant ($P < 0.05$).

The well documented relation between multiple sclerosis and uveitis is difficult to evaluate from a clinical point of view. Asymptomatic forms of ocular inflammation have been variously described in multiple sclerosis. The local production of IgG in the CSF of patients with multiple sclerosis is also well documented.⁴ White matter lesions on MRI of the brain are present in various inflammatory diseases, but specially multiple sclerosis.

The aim of this study was to check if the IgG concentration was increased in the aqueous humour of patients with idiopathic uveitis. The albumin quotient measures the modifications of the blood ocular barriers and by comparing both albumin and IgG quotient, the local production of IgG (IgG index) can be evaluated. The association between a high IgG index in aqueous humour and the presence of white matter lesions in patients with idiopathic uveitis and without neurological symptoms might be a phenomenon similar to the local increase in the IgG index in the CSF of patients with multiple sclerosis.

Our study is based on a quantitative measure of IgG production that is less sensitive than the qualitative measure of oligoclonal IgG. We think, however, that the large number of patients studied compensates for the lower sensitivity of our measures, compared with studies based on qualitative measures that involve a smaller number of patients.

The common presence of measles anti-

bodies in the CSF of patients with multiple sclerosis is well known.⁷ After adjusting for the values of measles optical density in aqueous humour, the correlation between IgG index and MRI remained significant. This indicates that measles optical density in aqueous humour and IgG index are positively linked with MRI but the link between IgG index and MRI lesions is only partially explained by the link between measles optical density in aqueous humour and MRI. If measles has a role in the origin of multiple sclerosis and multiple sclerosis related uveitis, it may not be the only contributing factor.

We acknowledge the Association pour la Recherche sur le Sclérose en Plaques (ARSEP).

SERGE KOSCIELNY
Département de statistiques médicales,
Institut Gustave Roussy,
Villejuif, France
PHILIPPE THULLIEZ
Laboratoire de la toxoplasmosse,
Institut de Pédicature,
Paris, France
EMMANUEL-ALAIN CABANIS
MARIE-THÉRÈSE IBA-ZIZEN
Service de Neuroradiologie,
CHNO des quinze-vingts, Paris, France
ELISABETH DUSSAIX
Laboratoire de Virologie,
CHU Bicêtre,
Le Kremlin Bicêtre, France
ETIENNE BLOCH-MICHEL
CLAUDINE TRICHET
LAURENT HELLEBOID
Unité d'immunologie oculaire,
CHU Bicêtre,
Le Kremlin Bicêtre, France

Correspondence to: Dr E Bloch-Michel, Unité d'immunopathologie oculaire CHU de Bicêtre, Faculté de médecine Paris Sud, Le Kremlin Bicêtre, France.

- 1 Bloch-Michel E, Helleboid L, Hill C, Koscielny S, Dussaix E. Measles virus antibody in aqueous humour of patients with uveitis associated with multiple sclerosis. *Lancet* 1992;339:750-1.
- 2 Bloch-Michel E, Iba-Zizen MT, Koscielny S, et al. MRI and idiopathic uveitis in: Dermouchamps JP, Verougstraete C, Caspers-Velu L, Tassinon MS, eds. *Recent advances in uveitis*. Amsterdam: Kugler, 1993:459-60.
- 3 Helleboid L, Dussaix E, Tounzi Y, Thulliez Koscielny S, Bloch-Michel E. The role of neurotropic viruses in the etiology of uveitis. In: Dermouchamps JP, Verougstraete C, Caspers-Velu L, Tassinon MS, eds. *Recent advances in uveitis*. Amsterdam: Kugler, 1993:253-6.
- 4 Waksman BH. Multiple sclerosis. *Curr Opin Immunol* 1989;1:733-9.
- 5 Quentin CD, Reiber H. Intraocular immunoglobulin G production in patients with perivascularitis of the retina and multiple sclerosis. In: Secchi AC, Fregona IA, eds. *Modern trends in immunology and immunopathology of the eye*. Milano: Masson, 1989:214-6.
- 6 Paty DW, Oger JFF, Kastrokoff LF et al. MRI in the diagnosis of MS. *Neurology* 1988;38:185.
- 7 Felgenhauer K, Schädlich HJ, Ackerman R. Cerebrospinal fluid virus antibodies: a diagnosis indicator for multiple sclerosis. *J Neurol Sci* 1985;71:291-9.

Central nervous system demyelination after vaccination against hepatitis B and HLA haplotype

Although very unusual, acute CNS complications may occur after vaccination against hepatitis B.¹ We report a patient with evidence of severe demyelination in the CNS after hepatitis B vaccination.

Local production coefficients in MRI+ and MRI- patients with uveitis

	MRI+ (n = 21)	MRI- (n = 47)	P value*
Albumin quotient	0.007 (0.003-0.011)	0.006 (0.003-0.013)	NS
IgG quotient	0.008 (0.006-0.024)	0.004 (0.002-0.011)	0.02
IgG index	1.33 (0.72-2.67)	0.74 (0.43-1.00)	0.002

*Wilcoxon test.

Results are medians (25th and 75th percentiles).