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Toxic leukencephalopathy following "ecstasy" ingestion

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Sirs: Ecstasy (3,4-methylenedioxymethamphetamine, MDMA, "XTC," "Adam," "E") is a popular oral recreational drug which has become established in the illegal drug scene. Since the late 1980s there have been a number of reports about complications associated with using this drug. A combination of direct toxicity and strenuous physical exertion can lead to various severe internal complications [1]. Because of the widespread and growing use of ecstasy we describe a newly observed, severe neurological sequela of observed but not biochemically confirmed ingestion of ecstasy.

A 19-year-old man with known previous occasional benzodiazepine and heroin use developed dizziness and lost consciousness the morning after having been reported to take ecstasy for the first time. The emergency physician found the patient already comatose with signs of respiratory insufficiency. He was incubated and ventilated and then transferred to the ICU of. Clinical findings on admission were monocular hematoma, pulmonary edema, and cutaneous emphysema but no focal neurological deficit; body temperature was normal. Serum analysis showed moderate elevations in white blood cell count, liver enzymes, and creatinine levels and a marked elevation in creatine kinase activity of 5500 U/l (MB 126 U/l) indicating rhabdomyolysis with renal failure. Toxicological analysis of body fluids, benzodiazepines, and amphetamines showed weakly positive results in both gastric aspirate and urine; other drugs were negative. The results of other routine laboratory blood and urine tests, abdominal sonography, and initial computed tomography were normal. The patient was weaned from the respirator without complications. Although he was awake, he did not react to noxious stimuli and showed no spontaneous movements. Computed tomography 2 and 3 weeks after admission revealed multiple hypodense lesions in the white matter.

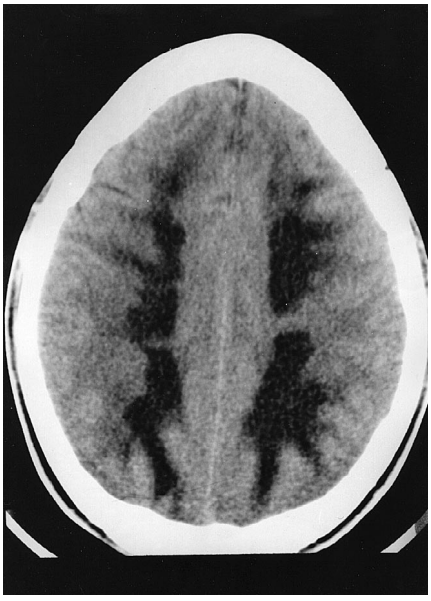

Fig. 1 Axial computed tomography shows extensive hypodensity of the white matter

One month after admission the patient was referred to our ICU for further evaluation. He showed a vegetative state with marked spasticity and intermittent unspecific reactions to noise with sustained generalized myoclonus; general physical examination was normal. Blood and urine examinations, including analysis of amino acids, fatty acids and their metabolites, were normal. CSF analysis revealed normal protein and normal cell count with lymphocytic activation and local IgG production. Electroencephalography showed generalized slowing with intermittent theta-wave activity. Computed tomography (Fig. 1) and magnetic resonance imaging (Fig. 2) revealed bilateral severe white matter damage.

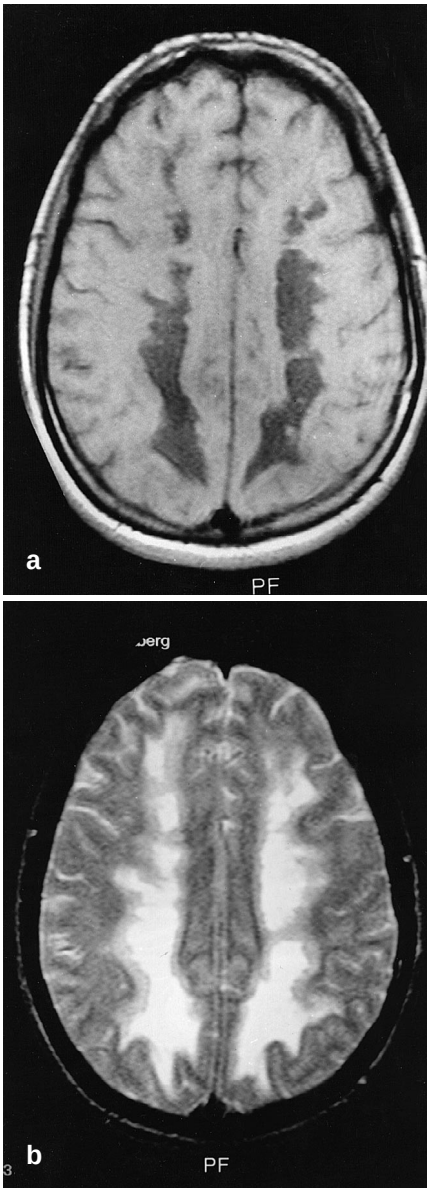

Fig. 2 **a** T1-weighted magnetic resonance image in the transverse plane shows bilateral, symmetric, low signal intensity of the white matter. The abnormalities are similar to those found on CT (Fig. 1). **b** T2-weighted image shows a high signal in the corresponding area. There is no tissue swelling indicating that the signal changes are due to abnormalities in the white matter and not due to brain edema. There is no loss of gray matter

The brain damage in this patient was restricted to the white matter. Selective vulnerability of myelin re-

sults from its specific chemical composition, with a high lipid content and very slow turnover. The myelinated tracts are thus particularly susceptible to the accumulation of lipophilic substances and to lipid peroxidation. There are essentially two possible etiologies: In one, selective myelin damage is present in lysosomal storage disorders such as sphingolipidoses, including metachromatic leukodystrophy, globoid cell leukodystrophy, and X-linked adrenoleukodystrophy [2]. However, age and acuity of manifestation, normal family history, and normal results of special laboratory analyses are not indicative of a metabolic disorder involving myelin metabolism. Secondly, toxic encephalopathy must be considered. Selective myelin damage can be caused by acute and chronic intoxication with lipophilic organic substances such as hexachlorophene, triethylene, and organic solvents as used by painters [2]. There are several reports of inhalation of preparations containing toluene ("glue sniffers") which caused diffuse focal white matter abnormalities and cerebral, cerebellar, and brainstem atrophy as detected by magnetic resonance imaging [3–5]. Extensive cerebral and cerebellar white matter spongiform change has been found at autopsy in European "heroin pyrolysate" smokers presenting with acute dementia, ataxia, quadriparesis, chorea, and blindness [6]. The toxic substance has not been identified. However, identical neurological and neuroradiological findings have been reported in cocaine addicts [2].

The patient presented here shows a pattern and course of neurological abnormalities which differ from these reports. Furthermore, forensic laboratory analyses and investigations of the local police exclude the possibility that heroin, cocaine, or organic solvents caused the encephalopathy. Cerebral hypoxia, which obviously had been present before admission, may cause a similar clinical picture and may also cause some white matter changes. However, hypoxia cannot be the only etiological factor in our patient, as indicated by the extent and pattern of leukencephalopathy present in our patient and by the lack of gray matter changes in vulnerable regions. We thus conclude that the ecstasy taken the night before admission caused the toxic encephalopathy, although the routine laboratory screening was not sensitive enough to detect this drug. Liver and renal failure, rhabdomyolysis, and pneumomediastinum correspond to reported sequelae, but toxic myelin damage has never been reported before.

Ecstasy might have caused such damage in a number of ways. In one study [7] neurodegeneration of axons in the serotoninergic system of animals, including primates, was attributed to the metabolites of ecstasy which oxidize to products that give rise to free radicals; these in turn induce oxidative stress and membrane damage [8] and thus myelin damage. However, the other consumers did not develop encephalopathy, and a special manifestating factor must therefore be postulated for our patient. Individual susceptibility may be related to abnormalities in the demethylation related to human debrisoquine hydroxylase [9]. We conclude that myelin damage in our patient may be an indirect sequel of MDMA mediated by both metabolic oxidative stress and multiorgan failure due to individual susceptibility. Severe, acute complications in susceptible persons, leading to early lethal outcome before such pronounced neuroradiological changes developed, may account for the rarity of reports of this complication. Furthermore, there may be other patients treated in urban hospitals who are clinically misdiagnosed as having hypoxic brain damage not confirmed by neuroradiological diagnosis.

On the other hand, such toxic damage following ingestion of ecstasy may have been caused by a lipophilic toxic contaminant, rather than MDMA as the causative toxic substance. Forrest has shown that the constituents of the designer drug ecstasy vary greatly and may be a mixture of various pharmacologically active and inactive substances [1].

We conclude that the use of ecstasy can lead to severe irreversible neurological deficit due to extensive bilateral hemispheric damage of the white matter as a rare but possibly underdiagnosed sequel.

References

1. Milroy CM, Clark JC, Forrest ARW (1996) Pathology of deaths associated with "ecstasy" and "eve" misuse. J Clin Pathol 49:149–153
2. Van der Knaap MS, Valk J (1995) Toxic encephalopathy. In: Magnetic resonance of myelin, myelination and myelin disorders. Springer, Berlin Heidelberg New York, pp 350–361
3. Ikeda M, Tsukagoshi H (1990) Encephalopathy due to toluene sniffing: report of a case with magnetic resonance imaging. Eur Neurol 30:347–349
4. Xiong L, Matthes JD, Li J, Jinkins JR (1993) MR imaging of "spray heads": toluene abuse via aerosol paint inhalation. AJNR Am J Neuroradiol 14: 1195–1199
5. Escobar A, Aruffo (1980) Chronic thinner intoxication: clinicopathologic report of a human case. J Neurol Neurosurg Psychiatry 43:986–994
6. Wolters ECH, Van Wijngaarden GK, Stan FC, et al (1982) Leukencephalopathy after inhaling "heroin pyrolysate." Lancet II:1233
7. Green AR, Cross AJ, Goodwin GM (1995) Review of the pharmacology and clinical pharmacology of 3,4,-methylenedioxymethamphetamine (MDMA, "ecstasy"). Psychopharmacology (Berl) 119:247–260
8. Colado MI, Green AR (1995) The spin trap reagent a-naphthyl-*N*-*tert*-butyl nitrone prevents "ecstasy"-induced neurodegeneration of 5-hydroxytryptamine neurons. Eur J Pharmacol 280:343–346
9. Tucker GT, Lennard MS, Ellis SW, et al (1994) The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). Biochem Pharmacol 47: 1151–1156

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