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Case Report

Chronic ecstasy (3,4-methylenedioxymetamphetamine) abuse: a recurrent and unpredictable cause of severe acute hepatitis

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Fifteen reports of hepatitis induced by ecstasy (MDMA, 3,4-methylenedioxymetamphetamine) have been published over the last 3 years. With the increasing enthusiasm for "Rave" parties, the incidence appears to be increasing, and is an important and often concealed cause of acute hepatitis in young people. We report two cases of recurrent ecstasy-associated hepatitis where the interval between drug consumption and jaundice was variable and the link therefore initially obscured. Liver biopsies of both patients showed acute hepatitis. One was of relatively mild degree, and the other was severe, with features suggesting auto-immune hepatitis. Both cases resolved spontaneously. A high index of suspicion and careful specific enquiry are necessary to make the diagnosis and warn the patient to abstain in future, since subsequent attacks may be fatal and insidious chronic damage may occur.

Key words: **Acute hepatitis; Ecstasy; Hepatotoxicity; Liver biopsy; 3,4-methylenedioxymetamphetamine.**

Ecstasy (MDMA) was first patented in 1914 by Merck as an appetite suppressant, but came to attention mainly as a mood-modifying drug in the 1970s. It has been listed as a class A drug of misuse since 1977 in the UK, and banned for clinical use in the USA since 1985 due to neurotoxicity. Well-recognised and potentially fatal side effects include cardiac dysrhythmias, fulminant hyperthermia, rhabdomyolisis and disseminated intravascular coagulation. However, recreational use of ecstasy has increased over the last decade, as it is perceived by the young to be safer than alcohol. It enables the user to dance tirelessly throughout the night, and induces a euphoric state of mind. Easily manufactured and aggressively black-marketed, different preparations have attractive names such as 'love-hearts', 'doves', 'icebergs', 'strawberries' and 'yellow kellys'. Each has its own enthusiasts, and the exact contents of them are open to speculation.

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The first seven reports of hepatitis associated with ecstasy use came in 1992 (1) and since then escalating numbers of sporadic case reports have confirmed this association (2–8). This report describes two patients with recurrent biopsy-proven hepatitis associated with chronic ecstasy use, and highlights the unpredictable timing and increasing severity of subsequent episodes.

Case Report

Case 1

A 19-year-old man was admitted to hospital with a sudden onset of nausea, dark urine, pale stools and jaundice. He had first started taking half an ecstasy tablet on Saturday nights 5 months previously, and over this period had gradually increased this to four tablets 2 nights per week. No alcohol or other drugs were consumed, and his supplier had stayed the same, although the tablets varied in size and colour weekly. Physical examination revealed jaundice but no signs of chronic liver disease or ascites.

Investigations showed a bilirubin of 131 μmol/l (normal 5–17 μmol/l), alanine transaminase 745 U/l (5–40 U/l), alkaline phosphatase 180 U/l (35–130 U/l), albumin 44 g/l (35–50 g/l), haemoglobin 14.9 g/dl, white blood cell (WBC) count 8.2×10^9/l and normal

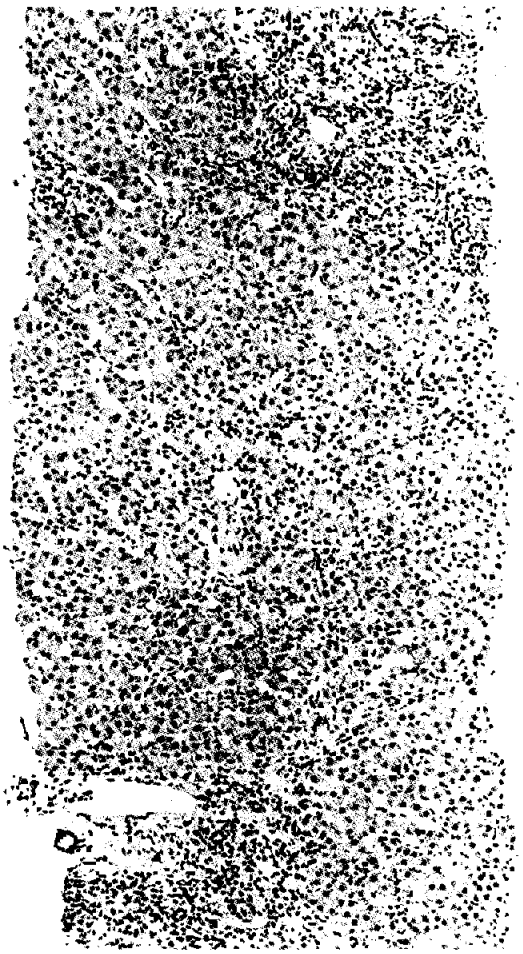

Fig. 1. Case 1. The biopsy shows two portal tracts (at the top and the bottom of the picture) expanded by a moderate inflammatory infiltrate predominantly composed of lymphocytes. A small terminal hepatic venule is seen in the centre of the photograph. The liver plate architecture is slightly distorted and there is mild parenchymal lymphocytic infiltration. This is an acute hepatitis of moderate severity. Hematoxylin and eosin. Magnification ×70.

coagulation screen. IgM antibody to hepatitis A virus, hepatitis B surface antigen, and second-generation RIBA testing for hepatitis C were all negative. Autoantibody screen, iron and copper studies and alpha-1 antitripsin were all negative. Ultrasound of the liver was normal. Liver biopsy revealed portal tract expansion by moderate inflammation consisting of lymphocytes mainly and including eosinophils (Fig. 1). Portal linking and early bridging necrosis, with mild parenchymal inflammation were also present. The appearance was of an acute hepatitis with drug toxicity as a possible cause.

The episode resolved gradually over 6 weeks, and his liver function tests were documented to return to normal. During this time he felt too unwell to attend Rave parties and thus to take ecstasy. Once better, he resumed his habit at three tablets per week, and 2 months later he changed his supplier. He then had a further episode of jaundice and was referred to the Royal Free Hospital hepatology unit. Examination findings were unchanged.

Liver function tests at this stage showed a bilirubin of 124 μmol/l (normal 5–17 μmol/l), alanine transaminase 780 U/l (5–40 U/l), alkaline phosphatase 197 U/l (35–130 U/l), albumin 45 g/l (35–50 g/l). Other investigations were unchanged and Epstein-Barr virus and cytomegalovirus IgM test were negative. Specific questioning revealed the history of ecstasy use, and he was strongly advised to discontinue ecstasy. The episode resolved spontaneously over 2 weeks, but he continues to take three tablets per month. His liver function tests remain mildly deranged as follows: bilirubin of 6 μmol/l (normal 5-17 μmol/l), alanine transaminase 340 U/l (5–40 U/l), alkaline phosphatase 130 U/l (35–130 U/l), albumin 45 g/l (35–50 g/l).

Case 2

An 18-year-old girl presented to her general practitioner with jaundice, malaise, dark urine and pale stools. She had first taken ecstasy 3 months previously, and had taken half a tablet per week at first. This dose had increased over 1 month, and 2 days after taking one and a half tablets, she had the first episode of jaundice, anorexia and lethargy. No alcohol or other drugs were used concurrently. Physical examination at this stage revealed no stigmata of chronic liver disease, and abdominal examination was normal.

Investigations showed a bilirubin of 96 μmol/l (normal 5–17 μmol/l), alanine transaminase 2435 U/l (5–40 U/l), alkaline phosphatase 176 U/l (35–130 U/l), albumin 40 g/l (35–50 g/l) and normal full blood picture and coagulation. IgM antibody to hepatitis A virus, hepatitis B surface antigen, and second-generation RIBA testing for hepatitis C were all negative. Autoantibody screen, iron and copper studies and alpha-1 antitripsin were all negative. Immunoglobulin profile was unremarkable with serum IgA 0.9 g/l (0.9–4.5 g/l), IgG 8.4 g/l (8–18 g/l) and IgM 1.7 g/l (0.6–2.8 g/l). Ultrasound of the liver was normal. The episode resolved spontaneously over 3 weeks, and hospital admission was not required.

She then re-started ecstasy at one and a half tablets per week with no apparent ill effects for 2 months, but 2 days after increasing the dose to two tablets, the second episode of jaundice occurred. Initial examination revealed a grade one encephalopathy and tender hepatomegaly 3 cm below the costal margin. Two

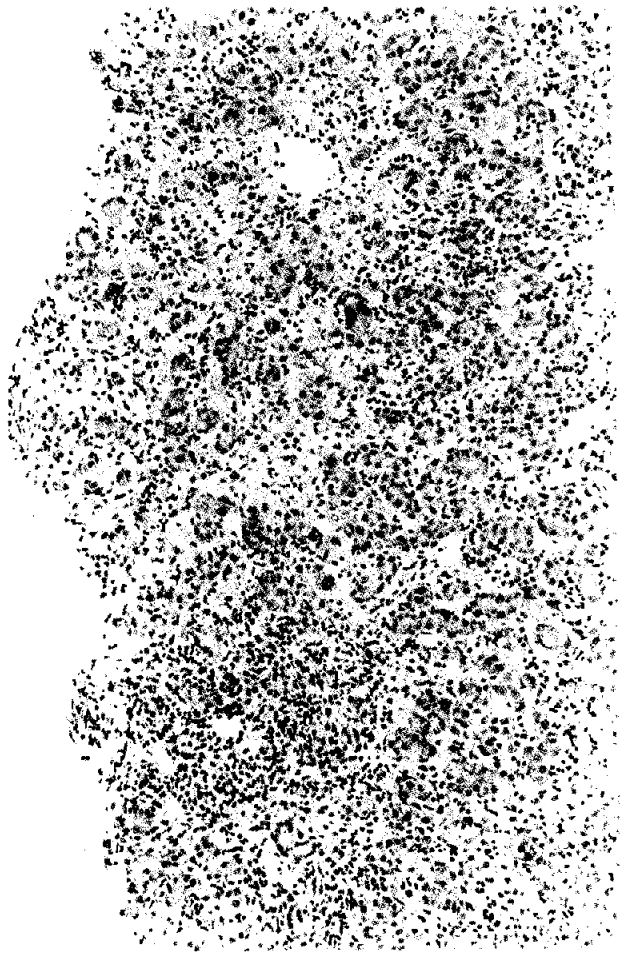

Fig. 2. Case 2. This liver biopsy shows a severe acute hepatitis. A portal tract is present in the lower left of this field, and it is expanded by an inflammatory infiltrate which has blurred the distinction between the portal tract and parenchyma. The inflammatory infiltrate includes lymphocytes, eosinophils and plasma cells (not discernible at this magnification). The terminal hepatic venule is seen in the upper middle of this picture, and the parenchyma in between shows marked disturbance of architecture, with small groups of liver cells forming hepatitic rosettes. There has been considerable liver cell loss in addition. Hematoxylin and eosin. Magnification ×70.

days later, marked fluid retention with ascites, peripheral oedema and 6 kg weight gain had occurred.

Investigations showed a bilirubin of 201 µmol/l (normal 5–17 µmol/l), alanine transaminase 2000 U/l (5–40 U/l), alkaline phosphatase 138 U/l (35–130 U/l), albumin 40 g/l (35–50 g/l) and normal full blood picture. The prothrombin time was 24 s (normal 11–15 s) and the international normalised ratio 2.5 (normal 0.9–1.2). Autoantibody screen was again negative, including soluble liver antigen (kindly performed by Professor M. Manns, Medizinische Hochschule, Hannover). Slit-lamp examination was normal. Ascites and diffuse hepatomegaly were confirmed on ultrasound examination and CT examination revealed a normal portal vein. Transjugular liver biopsy was performed and demonstrated marked inflammation and architectural distortion with periportal bridging and zone 3 necrosis (Fig. 2). The inflammatory infiltrate included lymphocytes, plasma cells, neutrophils and eosinophils. There was liver cell ballooning, hepatitic rosette formation, and some hepatocytes showed giant cell transformation. Mild canalicular cholestasis was present. The features were of an acute severe hepatitis, and bore similarities to an autoimmune hepatitis. Due to the severity of the liver failure and the delay in awaiting full autoantibody profile, prednisolone 30 mg daily was commenced, and the ascites managed with 100 mg daily of spironolactone for 1 week. The liver function tests returned to normal over 3 weeks, and the steroids were then stopped with no recrudescence of hepatitis. She no longer uses ecstasy and remains well, with normal liver function tests.

Discussion

The British rave counterculture continues apace, and there is evidence that it is spreading across the Atlantic (9). The young people who use ecstasy frequently believe that it is safer than alcohol, and do not view it as a drug of addiction. Easily synthesised, much of it is imported from The Netherlands, where the number of users has been estimated at 50 000 to 100 000 (5). The drug is packaged as an attractive, seemingly harmless, non-addictive mood enhancer and partygoers can choose from "weaker" preparations termed "love-hearts" or "doves" to stronger forms termed "double doves", "yellow kellys" or "Cali splits". Both our patients commented that the pills occasionally contained brown flecks, and the exact components of the tablet remain unknown. The evidence is strong that the MDMA component or its metabolites are associated with hepatitis, but the timing of the hepatic damage appears unpredictable and the aetiology is often initially concealed. Sadly, milder episodes of hepatitis may not be a sufficient deterrent to subsequent use, and chronic derangement of liver function can then result, as in our first case. The long-term outcome in this situation remains unknown, but fibrosis (4) and eventual cirrhosis are possibilities.

Henry et al. (1) described seven cases of hepatotoxicity related to ecstasy use, with jaundice up to 3 weeks following drug consumption. One patient had used ecstasy for 3 months before developing fatal liver failure, and another chronic user required liver

transplantation. The duration of abuse was not given for all patients, but the time from last taking ecstasy to clinical presentation varied from 1 to 3 weeks. They postulated that hepatotoxicity was possibly related to repeated exposure.

Three further cases of ecstasy-induced hepatitis were reported by Dykhuizen et al. (2). The interval between ingestion and jaundice varied from 3 days to 4 weeks, and all resolved spontaneously. Two of these patients had used ecstasy for the first time, whereas the third had taken it regularly for a year before his first attack of hepatitis. Liver biopsy was performed for one patient, and revealed an acute hepatitis compatible with drug toxicity. Five single case reports support the variability of the timing of the jaundice from around 1 week (4–6) to 4 weeks (3) from first ingestion of ecstasy.

Only two reports have been published of recurrent jaundice due to chronic ecstasy use. The first of these describes a 22-year-old woman who had used ecstasy six times in 6 months before her second episode of jaundice occurred. The second episode was more severe than the first, with evidence of ascites and coagulopathy, as in our second case (4). She was treated with prednisolone, and repeat liver biopsy showed extensive fibrosis. Shearman et al. (6) report a 27-year-old woman who used ecstasy on two occasions, 6 months apart. Each episode resulted in self-resolving jaundice, but the link with ecstasy was made by the patient herself.

Our experience highlights the unpredictable timing of both initial and recurrent ecstasy-induced hepatotoxicity. The pattern of use in our patients is of a gradually increasing dose taken weekly, and possibly of increasingly severe subsequent episodes of hepatitis. Patients rarely volunteer that they have taken ecstasy unless specifically asked in private, since it is not perceived as a dangerous drug. Biopsy appearances may mimic both viral (2) and auto-immune hepatitis, and there may be a role for corticosteroid therapy, as was given in our second case. If the initial aetiology of the jaundice is missed and the patient is not warned to avoid subsequent usage, fulminant hepatic failure may ensue. Ecstasy may turn out to be one of the small group of drugs that can cause insidious chronic hepatitis (10,11), and eventual fibrosis (4) and cirrhosis. We recommend that all young people with either a first or recurrent episode of acute hepatitis should be specifically asked about ecstasy use at any time in their past and be appropriately warned of the risks.

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