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BRIEF REPORT

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Liver transplantation for the treatment of fulminant hepatic failure induced by the ingestion of ecstasy

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Abstract Methylenedimethoxymethamphetamine (MDMA), more commonly known as ecstasy, is a synthetic amphetamine derivative used by teenagers and young adults in the United States as well as in Western Europe as a "dance drug". Though a number of complications associated with this drug have been reported, there is little information pertaining to hepatoxity as a result of MDMA ingestion. This case report is about an 18-year-old female patient who regularly used ecstasy on weekends over a 2-month period. Within 2 days after accepting a "hit" of the substance at a party, she was admitted to the hospital because of lethargy, vomiting, abdominal pain, stool discoloration, icterus, and darkened urine. On day 7 she developed fulminant hepatic failure with reduced hepatic coagulation factors and grade IV encephalopathy. Orthotopic liver transplantation was carried out 10 days following the ingestion. The patient made a full recovery within 72 h and was released from the hospital 6 weeks later. Histopathological examination of the removed liver revealed a nutritive-toxic liver necrosis. This case demonstrates that the ingestion of ecstacy, even on an infrequent basis, can lead to acute fulminant liver necrosis, and that this life-threatening complication can be treated successfully by liver transplantation.

Key words Ecstasy, fulminant hepatic failure, liver tranplantation · Fulminant hepatic failure, ecstasy, liver transplantation · Liver transplantation, fulminant hepatic failure, ecstasy

Introduction

Methylenedimethoxymethamphetamine (MDMA), more commonly known as ecstasy, is a synthetic amphetamine derivative used by teenagers and young adults in the United States as well as in Western Europe as a "dance drug". The drug is taken orally as tablets or capsules at doses of approximately 50–150 mg [7]. While the majority of occasional ecstasy users develop only mild side effects, a number of complications following

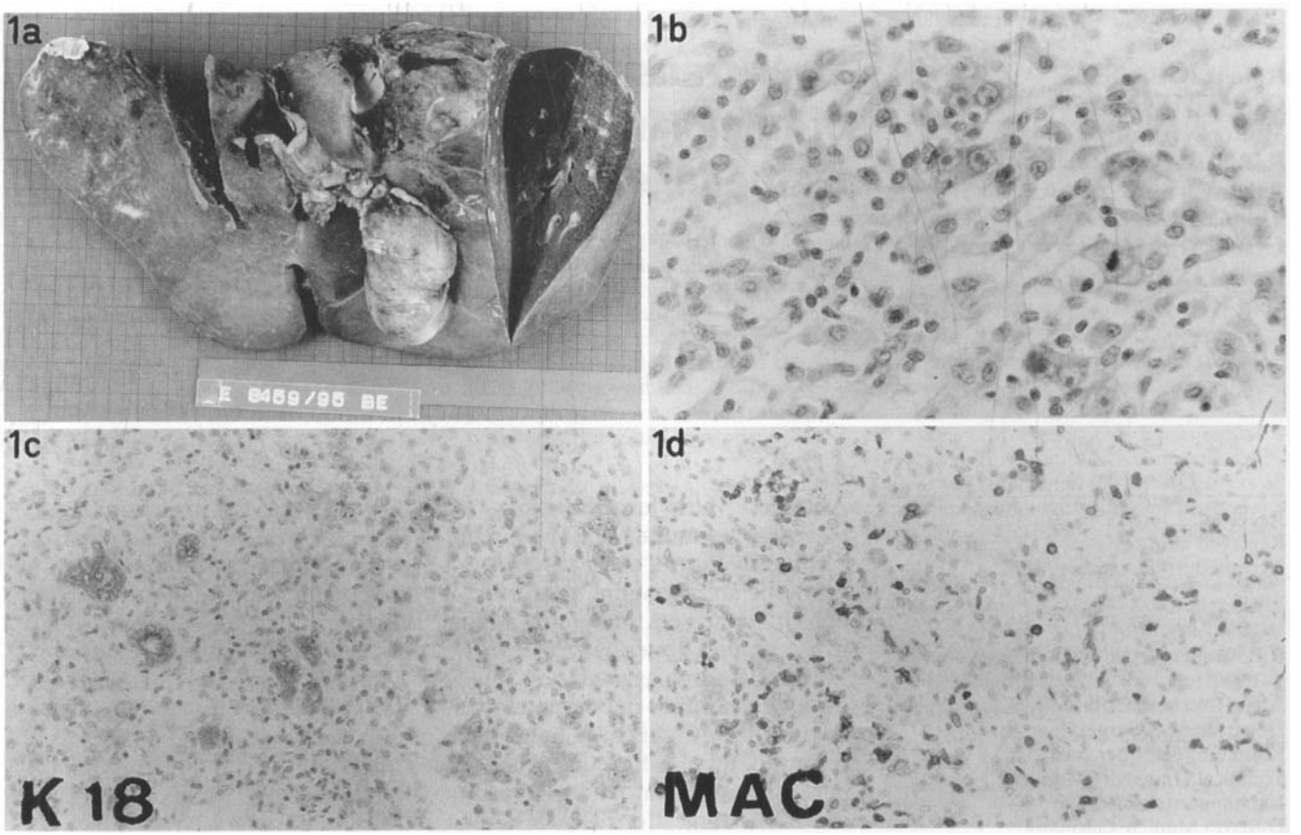

Fig. 1 **a** Macroscopic examination of the removed liver revealed a shrunken organ, only half its normal weight; on the cut surface, the parenchyma was firm, yellow-brown, with numerous, evenly distributed, shallowly depressed red spots that corresponded to the hyperemic and hemorrhagic lobular centers throughout the liver. **b** Histopathological examination revealed massive liver necrosis with almost total loss of hepatocytes, which were replaced by numerous macrophages, histocytes, and some chronic inflammatory cells. **c** Immunohistology for Keratin 18, which is normally found in hepatocytes and bile duct epithelium, showed reactivity in the original and regenerative bile ducts, in the widened portal tracts, and in the few remaining and regenerative hepatocytes within the former lobular area. **d** Immunohistology with the monoclonal antibody MAC387 showed many macrophages in addition to histiocytes and a few inflammatory cells within the former lobular areas. H&E, 40 × 1.6; K18: 25 × 1.6; MAC: 25 × 1.8

repeated ingestion of the drug have been reported. These complications have included disseminated intravascular coagulation [6], rhabdomyolysis [11], acute renal failure [5], and even death [2]. It has been recently observed that the repeated use of ecstasy can cause hepatic damage [8, 9]. Hepatotoxicity induced by the intake of ecstasy can be treated conservatively with patients making a full recovery [3]; however, in some cases, MDMA misuse can lead to fulminant hepatic failure with total loss of functional liver parenchyma, as well as encephalopathy, which can progress to cerebral edema and multiorgan failure [4, 8]. The prognosis with grade III–IV hepatic encephalopathy remains poor, with a mortality rate approaching 50 %–90 %. O'Grady et al. [10] described survival of approximately 12 % when drug-induced acute hepatic failure was treated conservatively. The present case report is about an 18-year-old female patient who regularly used ecstasy on weekends over a 2-month period and who developed acute liver failure requiring liver transplantation.

Case report

Six days after accepting a "hit" of ecstasy (one or two pills) at a techno-party, an 18-year-old female habitual weekend user, who had regularly ingested the drug over a 2-month period, was transferred to our institution from a community hospital for reasons of lethargy, vomiting, abdominal pain, stool discoloration, icterus, and darkened urine. Coagulation was pathologic with a Quick's test of 33 % and a APTT of 50 s. In the course of treatment, coagulation factors were replaced by fresh frozen plasma, as well as factors II, VII, IX, and X prothrombin, proconvertin, Stuart-Prower's factor, factor B (PPSB). On day 8 following ingestion, the patient fell into an agitated state and then went into coma, and was subsequently transferred to the ICU. The diagnosis of fulminant hepatic failure was documented clinically as well as from laboratory findings (bilirubin

263 µmol/l, ALAT 1530 U/l, NH4 186 µg/dl, lactate, 8.2 mmol/l; Fig. 2). Hepatic coagulation factors were significantly reduced (factor V < 5 %, antithrombin III CS to 36 % and fibrinogen to 139 mg/dl). Ultrasound and an abdominal CT showed a normal appearance of the liver parenchyma. The patient fell into a grade IV encephalopathy, breathing without ventilatory support, pupils were dilated with slow pupillary reflex, muscle hypotonus, and intermittent stretch convulsions of the upper extremities. In view of the rapid deterioration in her condition, she was immediately registered with the Eurotransplant Foundation at a high urgency status, whereby an organ became available within 24 h. Prior to transplantation, coagulation factors were replaced four to six times within a 24-h period by fresh frozen plasma and PPSB. On day 10 following ingestion, orthotopic liver transplantation was performed using the standard technique with venovenous bypass, simultaneous arterioportal reperfusion, and side-to-side bile duct anastomosis.

Macroscopic examination of the removed liver revealed a grey-white capsule and a firm yellow-brown parenchyma with many shallow, depressed red spots (Fig. 1 a). The histological picture was that of a subacute necrosis, mostly of lobules with hyperemic and hemorrhagic centers. Only very few hepatocytes, which were hydropic and necrobiotic, were recognizable on the H&E-stained section (Fig. 1 b). Immunohistologically, using a Keratin 18 antibody, which normally reacts with hepatocytes and bile duct epithelium, weak specific staining was seen in the few remaining hepatocytes in the periportal zone, along with a strong reaction within the large and the focally proliferating small bile ducts along the portal tracts (Fig. 1 c). The basic architectural pattern was maintained. The portal tract and central veins, however, were very close to each other, due to the loss of most liver cells and lobular collapse. There was only slight inflammatory infiltration within the remaining portal tracts. The lobular area was crowded with histiocytes and macrophages, recognizable by their immunohistological reactivity with the monoclonal antibody MAC387, which is specific for macrophages (Fig. 1 d). Some contained engulfed cell debris. Central veins were hyperemic and surrounded by erythrocytes and fibrin. Polymerase chain rejection for the viruses herpes simplex I/II and hepatitis C were negative. Immunohistologically, there was no hepatitis B antigen reactivity found. The biopsy of the transplanted liver revealed fatty changes in up to 40 % of the hepatocytes. Immunosuppression was maintained with oral FK 506, 2 mg/day, and urbasone, 8 mg/day.

Functional liver parameters (bilirubin, coagulation, and ammonia) during the pre- and postoperative course of transplantation are shown in Fig. 2. Liver function was determined by assessment of the microsomal function (Amonopyrin breathing test). Liver biopsies were taken to determine the status of immunological dysfunction. There were no measurable traces of MDMA detected at the time of transplantation. The patient made a full recovery within 72 h. Transaminases and bilirubin remained above normal for approximately 3 weeks due to the fatty changes in the donor liver. The patient was released from the hospital in excellent condition within 6 weeks of transplantation.

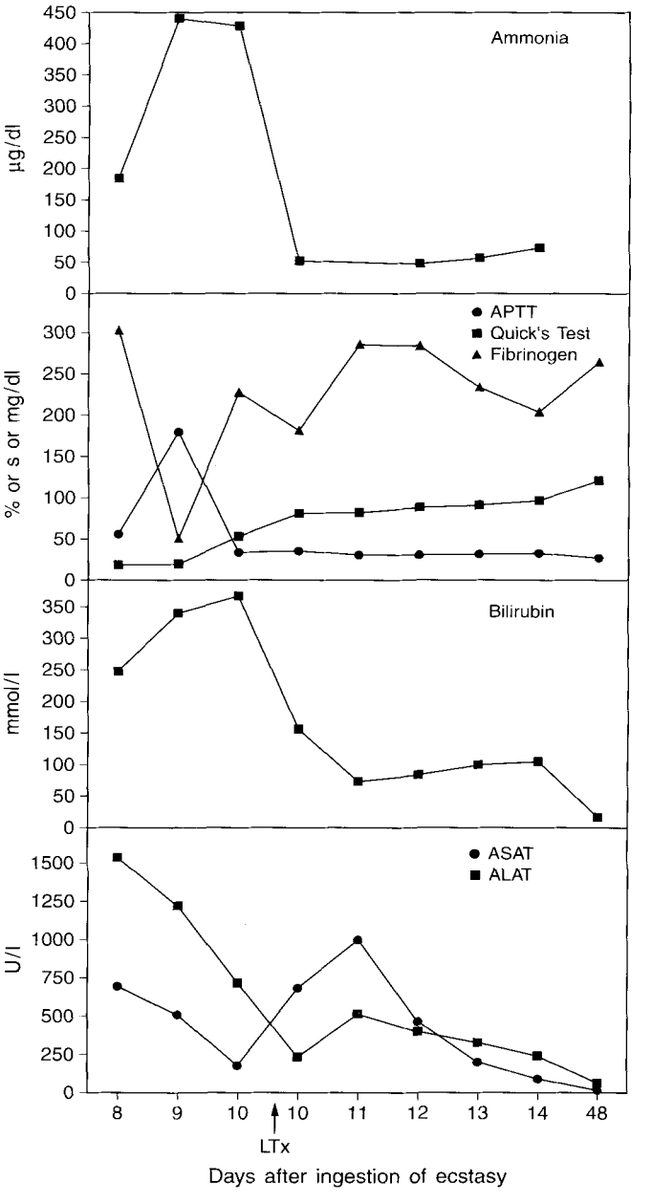

Fig. 2 Follow-up of liver enzymes and liver-synthesized proteins indicated by a functional coagulation test. Ingestion of one or two ecstasy pills was on day 0. Orthotopic liver transplantation was performed on day 10. Quick's test is expressed as a percentage, APTT in s, fibrinogen and bilirubin in mg/dl, ammonia in µ/dl, and ASAT and ALAT in U/l. Coagulation factors were substituted in the form of fresh frozen plasma and PPSB from day 4 to day 10

Discussion

Since the early 1990s, the number of ecstasy users in the United States and Western Europe has continued to increase among teenagers and young adults due to the drug's ability to maximize the "high" that enables one to dance for hours and its enhancing effects on sociability and euphoria.

Alarmingly, the exact toxic effect of MDMA remains unknown. There are reports on the wide range of side effects of frequent ecstasy abuse – mild ones, such as heat stroke, to the most extreme kind, death from fulminant liver disease [8] after the ingestion of only one or

Table 1 Clinical data available on ten cases after liver transplantation following ingestion of ecstasy

Case	Age and sex	Circumstances	Clinical course	Outcome	References
1	21 F	Took ecstasy and LSD at a party	Within 24 h severe coagulopathy (INR > 15); temp 41°C; renal failure; hyperacute liver failure	Liver transplant after 4 days; died of sepsis on day 13 post-transplant	Ellis et al. [4]
2	36 F	Took single capsule of ecstasy	Developed encephalopathy within 26 days; bilirubin 406 μmol/l; INR 6.5	Liver transplant after 31 days; died of sepsis on day 25 post-transplant	Ellis et al. [4]
3	22 F	6-month history of ecstasy	Bilirubin rose to 343 mmol/l, INR 4.1, grade II encephalopathy	Auxiliary left partial orthotopic liver transplant. Died of sepsis 30 days post-transplant	Ellis et al. [4]
4	24 F	Took 2–4 tablets of ecstasy 6 weeks prior to admission	Grade III encephalopathy, INR > 15; bilirubin 407 μmol/l	Received a reduced liver graft because of a mismatch in size. Successful.	Ellis et al. [4]
5	21 F	Took ecstasy tablets at party. Hyperactivity, progressing to convulsions	Repeated seizures; temp 41°C; pulse 170 bpm; BP 170/100; DIC, rhabdomyolysis, ARF	Liver transplant after 4 days, death from graft rejection after 18 days	Henry et al. [8]
6	19 M	History of MDMA misuse. No history of other drug intake	7 days after last dose of MDMA, increasing jaundice, vomiting, confusion, bilirubin 400 μmol/l	Fulminant hepatic failure required liver transplant. Successful	Henry et al. [8]
7	18 F	Took 1–2 ecstasy tablets at party. Progressing queasiness and abdominal pain	Progressing hepatic failure 8 days after last dose of ecstasy, bilirubin 263 μmol/l	Fulminant hepatic failure required liver transplant on day 10. Successful.	Present case
8	33[b]	Took unspecified amount of ecstasy	11-day interval between onset of jaundice and grade IV encephalopathy; bilirubin 642 μmol/l, DIC	Auxiliary liver transplantation. Remained graft-dependent 18 months after LT	Chenard-Neu et al. [1]
9	19[b]	Took unspecified amount of ecstasy	15-day interval between onset of jaundice and grade IV encephalopathy; bilirubin 6500 μmol/l, DIC	Auxiliary liver transplantation. Remained graft-dependent 5 months after LT	Chenard-Neu et al. [1]
10	18 M	Took ecstasy over a period of several months	Progressing hepatic failure	Fulminant hepatic failure required auxiliary liver transplant. Successful.	Erhard[a]

[a] Personal communication, 1996, Department of General Surgery, University Clinic, University of Essen, Germany
[b] Sex not mentioned

two pills. The mechanism of ecstasy-induced hepatic damage remains unclear. Histological findings range from moderate lobular hepatitis to massive necrosis, as seen in our case. The severity of liver damage does not seem to correlate with the amount or frequency of ecstasy intake, leaving one to assume that individual susceptibility is a major determinant.

The serological parameters of our patient for hepatitis or other liver diseases were negative. Hepatic failure developed within 3 days of ingestion and synthetic performance of the liver was markedly reduced, requiring replacement of plasma and coagulation factors. Only the APTT remained below 50 s because of the early replacement of hepatic coagulation factors. The fact that 10 days after the ingestion of ecstasy, no traces of MDMA could be detected in the serum and liver tissue of our patient would indicate that all of the MDMA was already fully metabolized at the time of liver transplantation, due to the short half-life of the drug. Histopathological examination of the recipient's liver revealed a massive liver necrosis with a subtotal loss of hepatocytes and only some regeneration. There is, as yet, no clear evidence that impurities or variations in the manufacture of ecstasy, or its combined intake with other drugs, are involved in the effects seen after the ingestion of ecstasy. Whether ecstasy is directly hepatotoxic in these cases, whether it causes liver injury over and above that resulting from hyperthermia, is still difficult to determine [4].

Reports pertaining to the hepatoxicity of ecstasy are, however, increasing [4, 8, 9]. Fulminant hepatic failure,

when induced by ecstasy, can progress to multisystem failure associated with a mortality rate of up to 50 % [4, 8]. In the few reported cases of recovery without transplantation, hepatic necrosis subsided and hepatic regeneration occurred, with the return of normal liver histology. Of the four cases of fulminant hepatic failure following the ingestion of ecstasy reported by Henry at al. [8], one patient died, one slowly recovered after conservative treatment, and two received liver transplants. While one of the liver transplants was successful, the other patient died of graft rejection. Recently, Ellis et al. [4] described eight other cases of acute hepatic failure induced by the ingestion of ecstasy. Three were treated conservatively; the remaining five required liver transplantation. One patient died before receiving a liver transplant, and three others died of sepsis within weeks following liver transplantation. Only one patient survived.

If heterotopic or auxiliary liver transplantation can be performed as an interim hepatic support, these patients can recover and avoid the lifelong immunosuppression necessary after liver transplantation [1]. Erhard (personal communication) reported on a 19-year-old male who also developed fulminant hepatic failure after the ingestion of ecstasy. This patient received an auxiliary liver transplant. After 6 weeks, the liver graft could be removed and the patient experienced a full recovery. Ellis et al. [4] also reported on a 22-year-old female who, after fulminant hepatic failure induced by the ingestion of ecstasy, received a left partial auxiliary liver transplant. Her initial postoperative recovery was good, but she died 30 days post-transplantion of sepsis. Recently, Chenrad-Neu et al. [1] wrote in a multicenter study about the outcome of 30 auxiliary liver transplantations after fulminant hepatic failure, two of them after the ingestion of ecstasy. Histological biopsies, however, revealed fibrous scarring. Tapering of immunosuppression was not achieved in those patients who remained graft-dependent 5 and 18 months after liver transplantation.

The evidence until now depicts ecstasy as anything but an innocent dance drug. Its ingestion, even as a "one-shot deal", can lead to severe complications, such as acute fulminant liver necrosis in a non-dose-dependent fashion. This life-threatening complication can be treated successfully by liver transplantation.

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