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CASE REPORT

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Differential diagnosis of postoperative liver failure in a 12-year-old child

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Abstract The case of a 12-year-old child who died of fulminant hepatic failure a few days after tonsillectomy is reported. Histological examination revealed large areas of massive centrilobular hepatic necrosis. Hepatotoxity of postoperatively administered paracetamol in high dosages combined with enflurane exposure is discussed as a cause for the hepatic failure. The fulminant clinical course could have been influenced by an infection with hepatitis G virus which was detected in liver tissue by in situ hybridisation and was probably transmitted via transfusion of blood plasma.

Key words Fulminant hepatic dystrophy · Paracetamol intoxication · Enflurane anesthesia · Hepatitis G virus infection

Introduction

Acute hepatic failure is an uncommon problem for the forensic pathologist but can be of considerable interest. The most common causes of fulminant hepatic dystrophy are poisoning by phalloides or carbon tetrachloride and hyperacute viral hepatitis. Liver damage, associated with renal failure and severe encephalopathy, can also be induced by paracetamol intoxication. Furthermore, severe postoperative hepatic dysfunction and acute necrosis of the liver have been observed following anesthesia with halothane, enflurane or isoflurane.

We report a case of a 12-year-old child who died in an acute hepatic coma 4 days after tonsillectomy and enflurane anesthesia. The possible causes of fulminant hepatic damage are discussed.

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Case report

A 12-year-old healthy girl underwent a tonsillectomy due to recurrent tonsillitis. General anesthesia was performed with thiopental, enflurane and nitrogen monoxide without any complications. In the first 4 days after surgery the patient received a total of 7,000 mg paracetamol (supp.), 140 mg codeine and individual doses of metoclopramide for treatment of recurrent nausea and vomitus. On the 2nd postoperative day the girl complained of vertigo and in the evening responsiveness was reduced. On the 4th postoperative day the girl became unconscious and a deep coma was diagnosed. The physical examination revealed no icterus, the liver and spleen were not palpable. The urinary output was reduced (about 15 ml/kg per hour, body weight 29 kg, height 146 cm) and cerebral edema was found in computerized tomography (CT).

Laboratory findings (4th postoperative day)

Hemoglobin content 9.9 g/dl, platelets 352,000/µl, prothrombin time (PT) 14%, partial thromboplastin time (PTT) 37 s, antithrombin III (AT III) 23%, fibrinogen fission products 1 mg/l, GOT 5,440 U/l, GPT 2,220 U/l, LDH 5,440 U/l, serum ammonia level 372 µmol/l, CK 611 U/l, creatinine 2.2 mg/dl, urea nitrogen 110 mg/dl (increasing), pH 7.16, pCO_2 26.2 mmHg, BE-17.9, oxygen saturation 95%.

Therapy (4th postoperative day)

Artificial respiration, infusion therapy, substitution of vitamine K (20 mg i.v.), fresh frozen plasma (FFP 2 IU), AT III (1,000 IU), prothrombin complex (PPSB 1 IU), buffering with sodium bicarbonate

Clinical course

Progressive signs of hepatic dysfunction, predominantly characterized by a disturbance of coagulation, continuous coma and renal failure. The patient was transferred to a special hospital on the 4th postoperative day for liver transplantation, but died in transit of multiple organ failure (MOF).

Postmortem findings

Autopsy: liver weight 1,200 g, tense capsule. The parenchyma was soft, fragile and yellow-tan. The skin and mucosae were icteric.

Multiple submucous and subserous petechiae, gastric hemorrhage (200 ml), pale and swollen kidneys and a diffuse encephalomalacia were found. The light microscopic examination showed massive centrilobular hepatic necrosis (Fig. 1).

Serological and virological investigations

Hepatitis A-IgM-antibodies (EIA), hepatitis B HBs-antigen (AGE), hepatitis B anti-HBc (EIA) were negative.

DNA/RNA analysis

Serum: hepatitis C virus-RNA, hepatitis G virus-RNA negative. Liver tissue: cytomegalovirus DNA negative, hepatitis C virus-RNA negative, hepatitis G virus-RNA positive (Fig. 2).

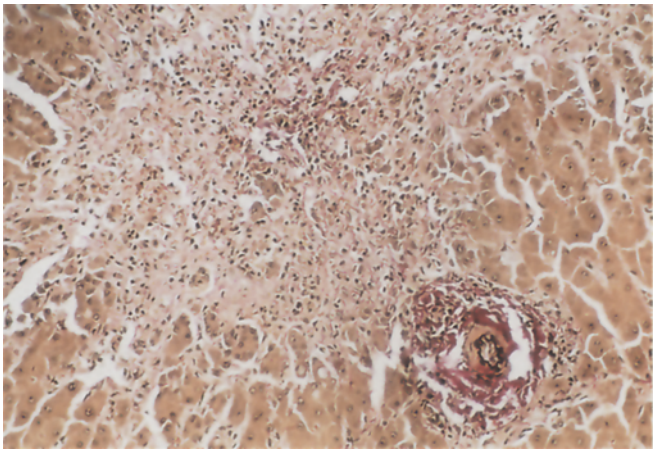

Fig. 1 Centrilobular necrosis with hepatic parenchymal collapse and mixed inflammatory infiltrate (EvG, × 150)

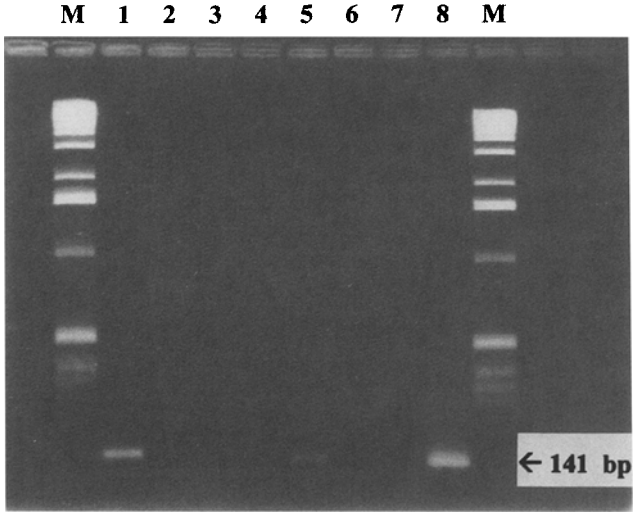

Fig. 2 PCR of hepatitis G virus with heminested primers in the NS3 region [24]. *Lane 1* Positive patient after bone marrow transplantation, *lane 2–4* negative patients, *lane 5* index patient (liver biopsy), *lane 6–7* negative controls, *lane 8* positive control. *Size marker* 1 kb-ladder. The expected product yields a size of 141 bp

Discussion

Acute postoperative hepatitis is usually caused by blood product transfusions, hypovolemic shock, or other factors of surgical stress [12]. Halocarbons can also induce severe liver damage, and the first anesthetic agent which was identified to be responsible for acute hepatic failure was chloroform [27]. In the case reported the fulminant hepatic damage may have different causes. Firstly enflurane exposure and/or high dosages of paracetamol could have induced a toxic liver damage. Secondly a fulminant viral hepatitis must be taken into consideration. Halogenated anesthetics such as halothane can induce severe hepatic dysfunction. About 900 cases of hepatic injury secondary to halothane have been reported [27]. Enflurane is also thought to be a possible cause of liver damage [9]. The pathogenesis of such liver damage is still unclear, and many factors have been considered such as hypersensitivity reaction [15], toxicity of intermediary metabolites [2, 18], multiplicity and duration of exposure [25], hypoxia, associated obesity [7], nutritional status [23], and prior induction of hepatic cytochrome P 450 by other substances (e.g. ethanol). Since enflurane and halothane have different molecular structures and physico-chemical properties [23], it seems probable that the comparable lower incidence of severe hepatic damage following enflurane exposure is related to the observation that only 2–3% of enflurane undergoes biotransformation compared to 15–20% of halothane [22]. Nevertheless enflurane might be hepatotoxic [8], but severe damage and death due to hepatic necrosis are extremely rare events [8, 17]. Isoflurane, an isomere of enflurane, has also been thought to be hepatotoxic in humans [3, 4, 14, 21] and to produce centrilobular necrosis in animals [23]. In the case reported no predisposing factors or a previous administration of halogenated anesthetics were known. Therefore, it is unlikely that the obviously lethal hepatic necrosis was exclusively caused by the anesthetic. On the other hand, at least a synergistic effect of high paracetamol dosages could have contributed to the rapid developement of hepatic damage [11]. The patient had a body weight of 29 kg and received a total of 7,000 mg paracetamol within the first 4 postoperative days, corresponding to a dosage of about 60 mg/kg, which is at the upper level of the recommended daily dosage in children. Toxic effects are known to occur if 150 mg/kg or more are given [6, 10], in particular if paracetamol is administrated within short time intervals. As the serum half-life of the active agent of paracetamol acetaminophen lies between 1.5 and 3 h, a maximum of up to 4–6 dosages a day are recommended in children or adults. In the reported case, five single applications a day are documented without further information on the time interval. The hepatotoxicity of high paracetamol dosages is explained by the limitation of metabolism by sulfation and glucuronidation leading to an increased metabolism by hepatic cytochrome p-450 to an unstable reactive product (N-acetyl-p-benzochinonimin) which is conjugated to intracellular glutathion. It has been shown in animal ex-

periments that reactive paracetamol metabolites can bind to cellular proteins leading to an induction of the membrane lipid peroxidase and production of toxic O_2-radicals which are assumed to be the damaging mechanisms [11]. Additionally, a toxic myocarditis following paracetamol intoxication is also described in the literature [24] but such a diagnosis could be excluded by histological examination in the case reported.

Serological and DNA/RNA investigations were negative for hepatitis B, hepatitis C. Cytomegaly virus DNA could not be detected in liver parenchyma using the method described by Bajanowski et al. [1] but there was evidence of hepatitis G virus-RNA in liver tissue detected by a heminested reverse transcription polymerase chain reaction (RT-PCR) assay [5, 26]. Direct sequencing of the 141 bp products from the RT-PCR confirmed the hepatitis G virus origin of the amplified sequences. The hepatitis G virus belongs to the family of *Flavi* viruses and has been associated with sporadic hepatitis [13, 20], fulminant hepatitis [26] and post-transfusion hepatitis [13]. It has a global distribution and is also present within the volunteer blood donor population [13]. Molecular evidence for transmission of hepatitis G virus by blood transfusion could be documented by sequence analysis [16, 19].

Since no signs of (mild) hepatitis were present in this case history, the application of AT III and FFP during intensive care might also have been the source of infection in our case. As AT III-products are pre-inactivated of hepatitis G virus, a transmission by FFP seems to be more probable. On the other hand the hepatitis G virus in this instance could have been a coincidental infection since liver dysfunction started before the first FFP had been given. Therefore, it has been concluded that the fulminant hepatic necrosis in the child was caused by a synergistic toxic effect of enflurane anesthesia and high dosages of paracetamol.

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