

## ALCOHOL-RELATED SUDDEN DEATH WITH HEPATIC FATTY METAMORPHOSIS: A COMPREHENSIVE CLINICOPATHOLOGICAL INQUIRY INTO ITS PATHOGENESIS

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**Abstract** — To clarify the pathogenesis of the widely known but obscure syndrome of sudden death with hepatic fatty metamorphosis observed in alcohol abusers, we have scrutinized both the clinical and pathological data of 11 subjects who died under such circumstances between 1987 and 1993. Death followed several days of uninterrupted drinking often with little dietary intake. The notable clinical features on arrival at the emergency room were disturbance of consciousness (11/11), hypotension (4/6), hypothermia (3/5), hypoglycaemia (8/11), metabolic acidosis (6/6), renal dysfunction (11/11), and hyperammonaemia (5/5). The common hepatic pathology was the extensive appearance of numerous microvesicular fatty droplets in the hepatocytes together with varying degrees of macrovesicular fatty change; four subjects had an underlying cirrhosis. Death undoubtedly results from a variety of metabolic disturbances triggered by the combination of massive ethanol intake and starvation. The appearance of extensive microvesicular fatty change superimposed on macrovesicular fatty change was considered to be an associated phenomenon

### INTRODUCTION

The mortality rate in individuals chronically abusing alcohol is several times that of the general population (Thorarinsson, 1979; Lindberg and Agren, 1988). It has been reported that about one-third of early deaths in middle-aged men are alcohol-related (Petersson *et al.*, 1982; Yuzuriha *et al.*, 1993). Furthermore, many of these individuals die suddenly (Petersson, 1988).

All cases of 'sudden death', occurring during the past 50 years in the Tokyo metropolis, were examined at the Tokyo Metropolitan Medical Examiner's Office, to determine the cause of death. In a previous study (Yuzuriha *et al.*, 1993) we showed that out of 534 chronic alcoholics who died suddenly of various diseases, 226 (42%) were categorized as 'a syndrome of alcohol-related

sudden death with alcoholic liver injury and hepatic fatty metamorphosis, but without other significant autopsy findings'. The causes of death in the remaining 308 subjects were variceal or upper gastrointestinal bleeding in 114 (21%), ischaemic heart disease in 66 (12%), cerebrovascular disease in 47 (9%), and other causes in 81 (15%) cases. The mechanisms of death in the majority of 226 cases determined to have died of 'a syndrome of alcohol-related sudden death with alcoholic liver injury and hepatic fatty metamorphosis, but without other significant autopsy findings' were not fully clarified even at autopsy.

Sudden death in alcohol abusers with hepatic fatty metamorphosis has been observed by forensic pathologists in various countries (Kuller *et al.*, 1974; Randall, 1980a; Copeland, 1985; Clark, 1988; Hansen and Simonsen, 1991). Nevertheless, the pathogenesis of such sudden death remains unclear (Randall, 1980b; Massello, 1984); this has been attributed to at least two factors; first that most of these sudden deaths are not witnessed (Petersson, 1988), contributing to the paucity of

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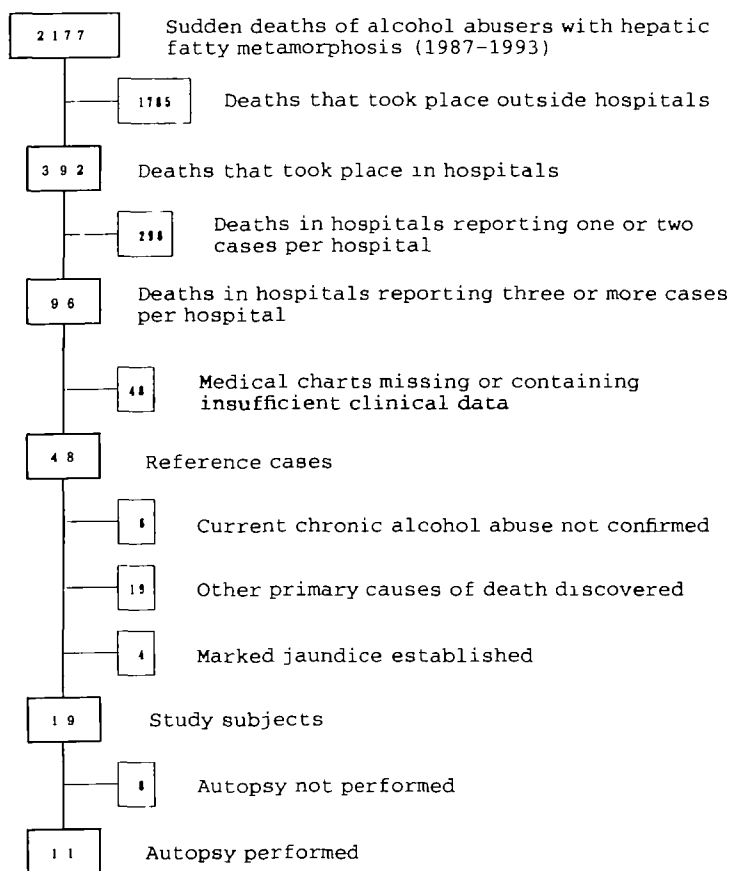


Fig. 1. Sequence of the systematic selection of study subjects.

clinical information essential in establishing the pathogenesis of such deaths and second that important metabolic disturbances present in life often defy detection at autopsy.

In an attempt to clarify the pathogenesis of 'alcohol-related sudden death with hepatic fatty metamorphosis (ASDHFM)', we have reviewed data from a selected group of such individuals initially admitted to a hospital emergency room in whom clinical and laboratory findings were adequately documented.

#### SUBJECTS AND METHODS

The sequence of our systematic selection of study subjects is detailed in Fig. 1. The final study subjects met the criteria for our definition of 'obscure ASDHFM', and in each case clinical,

laboratory, and autopsy information was available to allow elucidation of the pathogenesis of this syndrome.

Using the computerized database of the Tokyo Metropolitan Medical Examiner's Office, 2177 cases of ASDHFM occurring during the period 1987-1993 were identified. Twelve hospitals, each of which had treated at least three such individuals in their emergency rooms, a total of 96 cases in all, were contacted and further information requested. Data sufficient to determine the cause of death were obtained for 48 individuals. The remaining 48 subjects were excluded because their medical charts were either missing (21) or did not contain sufficient clinical data to evaluate and determine the cause of death (27).

Individuals were diagnosed as having 'obscure ASDHFM' if they had a history of chronic alcohol

abuse and were drinking heavily at the time of admission and if they died within 24 h of arrival in the emergency room. Patients were excluded if there was a well-established primary cause of sudden death, or if they were jaundiced with a serum total bilirubin  $\geq 200 \mu\text{mol/l}$ .

Of the 48 patients 19 were excluded because of a well-established primary cause of death viz: severe hypothermia (5), gastrointestinal bleeding (3), severe hyperkalaemia ( $K \geq 7 \text{mmol/l}$ ) (3), severe hypokalaemia ( $K \leq 2 \text{mmol/l}$ ) (2), diabetic hyperglycaemia (1), marked emaciation (1), meningitis (1), tension pneumothorax (1), severe insulin-induced hypoglycaemia (1) and cerebral haemorrhage (1). A further six patients were excluded because their current drinking behaviour was not adequately documented, while a further four individuals were excluded because they were severely jaundiced. Of the remaining 19 cases, 11 were autopsied while eight were not. As the main purpose of this study is the clinicopathological investigation of 'obscure ASDHFM', the 11 autopsied cases are considered as the principal study subjects while the eight non-autopsied cases are considered as supplementary study subjects.

Data were obtained from (1) ante-mortem clinical findings noted in the medical and inspection records, (2) laboratory data on admission, (3) clinical course and details of treatment in the emergency room, (4) autopsy reports, (5) microscopic re-examinations of histology slides, and (6) toxicological examination reports in the 11 autopsied cases. All data in this report are shown as mean values  $\pm$  SD.

## RESULTS

### *Autopsied cases*

The clinical and autopsy findings in these 11 subjects are summarized in Table 1.

*Conditions prior to arrival.* Two of the 11 subjects were found with clouded consciousness in their residences by acquaintances; two were found drunk in the streets and were under police protection; and one was found immobile in the street, all had a history of chronic alcohol abuse and were drinking heavily up to the time of admission. The remaining six subjects were found in a confused state at home by family members who provided further detailed information on the

subjects' drinking behaviour; all were chronic alcohol abusers and had drunk for two to 10 successive days prior to admission, hardly taking any food and water. Four subjects vomited frequently. No subject died from exposure to extreme atmospheric cold. One diabetic subject who was included in the study was on dietary therapy alone but no subjects including this particular subject were taking hypoglycaemia-inducing agents other than ethanol.

*Physical findings on arrival.* All individuals showed disturbed consciousness. Cardiac arrest had occurred in five individuals while in the ambulance immediately prior to admission; four further individuals were hypotensive (systolic BP  $\leq 90 \text{mmHg}$ ). Three individuals were hypothermic ( $\leq 35^\circ\text{C}$ ).

*Laboratory data.* No abnormalities were found on chest and abdominal X-ray examination in any of the subjects. No primary fatal arrhythmias or ischaemic changes were recorded in the electrocardiograms in any of the six individuals who had not experienced cardiac arrest.

The most striking laboratory findings were profound hypoglycaemia and severe metabolic acidosis. The mean serum glucose level was  $1.5 \pm 1.3 \text{mmol/l}$ ; hypoglycaemia ( $\leq 2.2 \text{mmol/l}$ ) was observed in eight individuals (73%) and was profound ( $\leq 1.1 \text{mmol/l}$ ) in seven (64%). Excluding the five individuals who had arrested prior to arrival severe acidaemia (arterial pH  $< 7.2$ ) was found in five individuals. Arterial oxygen pressure was above 90 mmHg in all 11 individuals. All 11 subjects showed severe metabolic acidosis (base excess  $< -10 \text{mmol/l}$ ). Urine ketones were positive in one of three individuals tested.

Elevations of serum urea nitrogen ( $> 6.5 \text{mmol/l}$ ) and serum creatinine ( $> 110 \mu\text{mol/l}$ ) concentrations were found in 10 (91%) and 11 individuals (100%) respectively. Plasma ammonia nitrogen was elevated above  $50 \mu\text{mol/l}$  in the five individuals in which it was measured. The mean values of other laboratory data were  $60 \pm 13 \text{g/l}$  for serum total protein,  $9.4 \pm 3.6 \times 10^9/\text{l}$  for white blood cell count, and  $11.2 \pm 1.9 \text{g/dl}$  for haemoglobin.

*Clinical course.* The mean time from arrival at the hospital to death was  $13 \pm 8 \text{h}$ . All individuals received intensive medical treatment in the emergency room. In most instances, fluids containing vasopressor drugs, vitamins and dextrose

Table 1. Clinical, laboratory, and autopsy findings in 11 alcohol-related sudden death victims

Case No.	Age (years) /Sex	Family /Job	Physical findings			Laboratory data								Findings at autopsy			
			Conscious level	SBP (mmHg)	BT (°C)	BS (mmol/l) (3.9–5.8)	TB (µmol/l) (2–18)	AST (U/l) (0–35)	NH <sub>3</sub> -N (µmol/l) (5–50)	Cr (µmol/l) (50–110)	Na <sup>+</sup> /K <sup>+</sup> (mmol/l) (135–145) (3.0–5.0)	Arterial pH	Urine ketones	Liver histology	BAC (mmol/l)	Other findings	
1	54/M	-/-	Stupor	58	32.8	0.7	NE*	188	80	120	133	4.1	7.12	-	LC	0	
2	55/M	-/-	Stupor	90	NE	2.8	48	1 183	NE	240	143	4.6	7.16	NE	FL	2	Chronic pancreatitis
3	49/M	+/+	Stupor	108	NE	0.6	118	750	55	260	134	3.6	7.29	NE	LC	0	Wernicke's encephalopathy
4	56/M	+/+	Coma	60	35.7	2.2	22	201	255	260	149	4.9	6.66	-	FL	NE	Pancreatic fibrosis
5	59/M	-/-	Coma	70	35.5	0.7	128	705	340	370	137	6.9	7.18	NE	LC	4	Chronic pancreatitis
6	64/M	-/-	Coma	100	32.0	0.6	180	431	NE	120	124	4.5	7.09	NE	FL	5	
7	61/M	+/-	Coma	CA	NE	0.6	18	193	NE	490	129	6.2	6.60	NE	FL	45	
8	48/F	+/-	Coma	CA	NE	0.4	46	2 790	NE	360	140	4.2	6.66	+	FL	8	Pancreatic fibrosis
9	63/M	+/-	Coma	CA	30.0	3.7	30	250	600	190	130	5.4	6.62	NE	LC	4	Pancreatic fibrosis
10	53/M	-/-	Coma	CA	NE	3.8	18	538	NE	390	139	3.5	6.99	NE	FL	0	Pancreatic fibrosis
11	50/M	+/-	Coma	CA	NE	0.6	34	252	NE	270	122	6.0	NE	NE	FL	8	Pancreatic fibrosis

SBP = systolic blood pressure; BT = body temperature; BS = serum glucose; TB = serum total bilirubin; AST = aspartate aminotransferase; NH<sub>3</sub>-N = plasma ammonia nitrogen; Cr = serum creatinine; BAC = blood alcohol concentration; M = male; F = female; NE = not examined; CA = cardiac arrest had occurred immediately prior to arrival; LC = liver cirrhosis; FL = fatty liver.

\*Jaundice specifically reported as absent in the inspection record in this case.

Table 2. Clinical and laboratory findings in eight alcohol-related sudden death victims who were not autopsied

Case no.	Age (years) /sex	Family /job	Physical findings			Laboratory data								
			Conscious level	SBP (mmHg)	BT (°C)	BS (mmol/l) (3.9–5.8)	TB (µmol/l) (2–18)	AST (U/l) (0–35)	NH <sub>3</sub> -N (µmol/l) (5–50)	Cr (µmol/l) (50–110)	Na <sup>+</sup> /K <sup>+</sup> (mmol/l) (135–145) (3.0–5.0)	Arterial pH	Urine ketones	
1	68/M	+/-	Stupor	80	34.7	1.7	54	134	95	170	117	5.7	6.93	+
2	50/M	-/-	Coma	84	38.3	1.1	28	1.415	NE	300	127	3.4	7.10	NE
3	56/M	+/+	Stupor	152	36.3	NE*	34	181	NE	110	124	3.2	NE	-
4	65/M	+/-	Coma	66	38.8	2.9	44	398	NE	230	144	4.2	6.85	NE
5	54/M	-/-	Stupor	Low†	24.3	1.1	30	299	485	310	145	3.8	6.52	+
6	61/M	-/-	Coma	CA	33.4	1.4	108	1.809	NE	320	129	6.2	6.95	+
7	40/M	+/-	Coma	CA	NE	0.9	42	71	235	210	133	6.2	NE	NE
8	46/M	-/-	Coma	CA	NE	0.1	22	783	595	340	142	5.0	NE	NE

Abbreviations as in Table 1.

\*Level of serum glucose after massive glucose infusion was 6.6 mmol/l in this case.

† 'Low blood pressure' was reported with no specific blood pressure reading.

were provided i.v. Transient improvement in the level of consciousness was accomplished in four patients with hypoglycaemia following i.v. administration of large doses of dextrose. Four of the five patients that had arrested were resuscitated once in hospital. Most of the 11 cases remained hypotensive until death.

**Autopsy and histopathologic findings.** The most striking findings in the liver were extensive microvesicular fatty change within hepatocytes and the presence of megamitochondria.

For clarity, we differentiated the patterns of fat deposition in the hepatocytes in terms of fatty droplet size and amount and grouped them into three types, type I: predominantly macrovesicular; type II: evenly mixed micro-/macrovesicular; and type III: predominantly microvesicular. Type I was observed in two, type II in seven, and type III in two cases. The microvesicular fatty droplets were diffusely distributed in the hepatic lobule (Fig. 2). In the two patients with type I change, microvesicular fatty droplets were found both in hepatocytes free of large fat droplets and within peripherally displaced hepatocytic cytoplasm. Megamitochondria were observed in autopsy material in nine subjects. Four subjects had established cirrhosis; none showed features of acute alcoholic hepatitis.

Deposition of microvesicular fatty droplets in the renal tubular epithelia was a common finding. There was no evidence of alcoholic cardiomyopathy or of acute haemorrhagic pancreatitis. Neuronal loss and gliosis of the mammillary bodies, determined as a sequela of Wernicke's encephalopathy, was found in one individual. Characteristic micro-anatomical changes related to hypoglycaemia were not found in the brains of any of the 11 subjects.

**Toxicological examinations.** Blood-alcohol concentrations, measured in heart blood at the time of autopsy were positive ( $45 \geq \text{BAC} \geq 1 \text{ mmol/l}$ ) in seven of the 10 subjects tested. Toxicological examinations revealed no toxic substances in either the stomach contents or blood.

#### Cases not autopsied

The clinical and laboratory findings in the eight subjects who did not undergo autopsy were almost identical to those of the 11 autopsied subjects (Table 2). One subject (Case No. 8) was diabetic, but was not receiving treatment. Four subjects

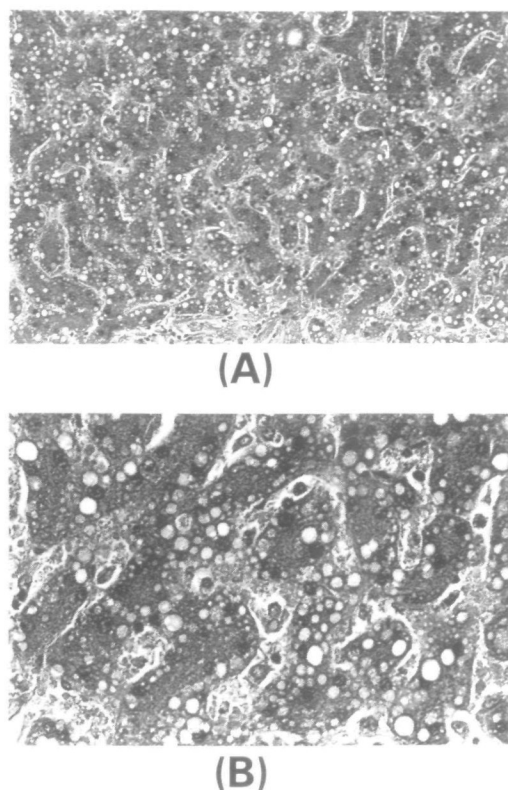


Fig. 2. Photomicrographs showing type III fatty liver. (A) Numerous microvesicular fatty droplets are present in hepatocytes throughout the hepatic lobule and a smaller number of macrovesicular droplets are detectable concomitantly (H & E,  $\times 150$ ). (B) A high power view ( $\times 400$ ) of part of (A).

living with their families were reported to have been drunk continually for more than several days prior to admission. Hypoglycaemia ( $\leq 2.2 \text{ mmol/l}$ ) was found in six of the seven subjects assessed and urine ketones were detected in three hypoglycaemic subjects. No significant abnormalities were found in chest and abdominal X-ray examinations, or electrocardiograms in any of the eight subjects.

#### DISCUSSION

Our discovery of the occurrence of severe metabolic disturbances, such as hypoglycaemia and metabolic acidosis, and the extensive presence of microvesicular fatty droplets in the hepatocytes

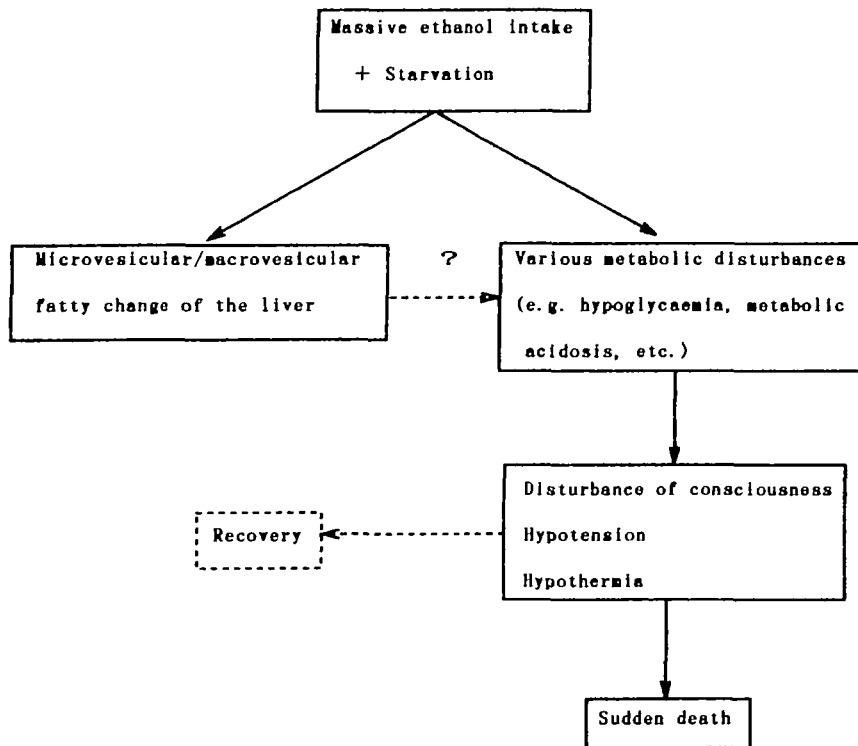


Fig. 3. Proposed pathogenetic mechanisms of alcohol-related sudden death with hepatic fatty metamorphosis.

and in the renal tubular epithelia may provide new insights into the pathogenesis of 'obscure ASDHFM'.

Hypoglycaemia was observed in eight (73%) of the 11 autopsied cases and in six (75%) of the eight non-autopsied cases, and was profound in 11 subjects (58%) overall. Although hypoglycaemia has been suspected to play a major causal role in alcohol-related sudden death syndrome (Randall, 1980*b*; Massello, 1984), there has been little evidence in the literature to substantiate this hypothesis. The importance of the role of hypoglycaemia in the development of the disturbance of consciousness was evident at least in four subjects who improved after i.v. administration of dextrose.

Two major factors have been considered contributory to ethanol-induced hypoglycaemia (Arky and Freinkel, 1966; Madison, 1968) suppression of hepatic gluconeogenesis resulting from an increase in the NADH/NAD<sup>+</sup> ratio accompa-

nied by enhanced ethanol metabolism, and depletion of hepatic glycogen storage secondary to starvation. All subjects in the present study had been drinking heavily often with little food and water intake, and frequently vomiting in the days prior to admission.

Ketones were detected in the urine in one of three cases in the autopsied group and three out of four subjects examined in the non-autopsied group. In cases of alcohol-related sudden deaths  $\beta$ -hydroxybutyrate levels are significantly elevated in the vitreous humour (Denmark, 1993), urine (Denmark, 1993), and blood (Thomsen *et al.*, 1995). Platia and Hsu (1979) described five non-diabetic alcohol abusers with hypoglycaemic coma and ketoacidosis and contended that the combination of alcohol-related hypoglycaemia and ketoacidosis may be common. Lactic acidosis is also known to occur in alcohol abusers (Campbell, 1984; Fulop, 1989). Serum  $\beta$ -hydroxybutyrate and lactate concentrations were not

measured in our subjects but were most likely elevated.

Elevations in serum urea nitrogen, creatinine, and ammonia nitrogen concentrations were also noted. It is difficult to determine whether these findings were a consequence of the microvesicular fatty change in the kidneys and liver, or a consequence of dehydration and hypotension.

Hypothermia may have arisen in relation to hypotension, hypoglycaemia, or severe metabolic acidosis, or at least in part, from the loss of body heat in the patients who had been left unconscious or intoxicated. The temperature was not documented in eight subjects; it was not measured in four subjects who arrested and was not measurable in the remaining four due partly to the lower reading limit on the thermometer being 35°C.

The most striking and common histological finding was the extensive appearance of numerous microvesicular fat droplets in hepatocytes together with macrovesicular fatty change in some. The former is considered to be evidence of acute alcoholic injury to the liver (Uchida *et al.*, 1983) and the latter to be evidence of chronic alcohol exposure. Morgan *et al.* (1978) described only three alcoholics with fatty liver and hepatic failure. They noted the presence of fine vacuolation in the hepatocytes and suspected that this might have represented damage to the hepatocytic organelles. Later Uchida *et al.* (1983) provided electron-microscopic evidence that the hepatocytes with foamy fatty change had extensive disorganization of the organelles (e.g. smooth endoplasmic reticulum, rough endoplasmic reticulum, mitochondria, etc.). Rosmorduc *et al.* (1992) described anecdotally four cases of alcohol-related sudden death with massive mixed microvesicular/macrovesicular fatty metamorphosis of the liver, and suspected that the massive existence of microvesicular fat in hepatocytes might be linked aetiologically to sudden death.

Through our systematic and comprehensive clinicopathological investigation, we have concluded that various metabolic disturbances triggered by the combination of massive ethanol intake and starvation are the most probable causes of 'obscure alcohol-related sudden death with hepatic fatty metamorphosis', and that the appearance of extensive microvesicular hepatic fat droplets superimposed on various degrees of macrovesicular fatty change is an associated

phenomenon of massive ethanol intake and starvation (Fig. 3). The possibility that the various metabolic disturbances might be directly related to microvesicular fatty change of hepatocytes remains (Fig. 3).

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