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ORIGINAL ARTICLE

Alcoholism and the Armanni–Ebstein lesion

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Abstract The Armanni–Ebstein lesion is a histological change in the kidney consisting of sub-nuclear vacuolation of the proximal tubules. It has been most associated with diabetic ketoacidosis. The vacuoles have been reported to contain glycogen. More recent studies show them to contain fat. Recent papers have associated the Armanni–Ebstein lesion with non-diabetic ketoacidosis. We present 11 cases of alcoholic ketoacidosis where the Armanni–Ebstein lesion was identified. None had a history of diabetes mellitus and none showed any changes of diabetic nephropathy. All 11 cases had raised acetone levels (3–67 mg/100 mL (mean 17.9 mg/100 mL and median value of 16 mg/100 mL). In addition a case of isopropanol poisoning was found to have the Armanni–Ebstein lesion. Isopropanol is converted to acetone but is not associated with acidosis. These results indicate that the Armanni–Ebstein lesion is not specific to diabetes mellitus.

Keywords Armanni–Ebstein · Alcoholism · Histology · Ketoacidosis · Acetone

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Introduction

The Armanni–Ebstein lesion was first reported in 1877 by Armanni and in 1882 by Ebstein and it has been associated with diabetic ketoacidosis [1]. The lesion consists of sub-nuclear vacuolation of the proximal tubules of the kidneys. Previous studies reported the vacuoles contained glycogen, more recent work shows that the vacuoles contain fat [2–4]. Diabetic ketoacidosis has long been associated with the Armanni–Ebstein lesion, Thomsen and colleagues reported fat in the kidneys in alcoholics [5] and Milroy and Parai reported a case of Armanni–Ebstein lesion in a non-diabetic child with ketoacidosis associated with starvation [6].

Whilst most commonly encountered in diabetics, ketoacidosis is seen in other situations including alcoholic ketoacidosis, high fat diets and starvation [7]. When carbohydrates are not available as an energy source, fat becomes the main energy source. Large quantities of fatty acid become available and fatty acids are converted to ketone bodies, that is, acetoacetic acid, ß-hydroxybutyrtae and acetone. Measurement of these substances at autopsy provides the basis for the diagnosis of ketoacidosis post-mortem [8–12].

We report an association between alcoholic ketoacidosis and subnuclear vacuolation (Armanni–Ebstein lesion) in the kidneys and a case of isopropanol poisoning with the Armanni–Ebstein lesion.

In periods of starvation in alcoholics, often compounded by vomiting, fatty acids cannot be oxidised and a surplus of acetyl-Co-A occurs. This is ultimately converted to aceto-acetic acid, some of which is decarboxylated to acetone and some reduced to β-hydroxybutyrate. The result of the accumulation of β-hydroxybutyrate, acetoacetic acid and acetone in non-diabetic alcoholics is alcoholic ketoacidosis. To identify alcoholic ketoacidosis, the β-hydroxybutyrate

concentrations can be measured in blood, including at autopsy [12]. Acetone profiles may also be identified when examining ethanol concentrations and acetoacetate may also be measured. Jones and colleagues found the median value for blood acetone in healthy blood donors was 0.126 mg/100 mL (97.5 centile ranges 0.037–0.469 mg/100 mL) [13]. Brinkmann and colleagues recorded acetone concentrations in 9 deaths with alcoholic ketoacidosis between 7.4 and 40 mg/100 mL (mean 18.3 mg/100 mL [14]. They stated that a blood acetone concentration above 9 mg/100 mL was evidence of death from alcoholic ketoacidosis. Normal β-hydroxybutyrate concentrations have been recorded up to 650 μmol/l (1 μmol/ = 0.104 μg/l) and acetoacetate up to 226 μmol/l. Concentrations of β-hydroxybutyrate in blood below 500 μmol/l are considered normal, those between 500–2,500 μmol/l elevated and those above 2,500 μmol/l pathological [12]. Isopropanol is formed by conversion of acetone, as well as being present when directly ingested and may be present in death from alcoholic ketoacidosis.

Methods

Cases with a diagnosis of alcoholic ketoacidosis were reviewed from the Provincial Forensic Pathology Unit in Toronto Ontario and the Eastern Ontario Forensic Pathology Unit, both units of the Ontario Forensic Pathology Service. In each case a full autopsy was performed with histology of the major organs and toxicology for alcohols was performed. As well as ethanol, acetone and isopropanol concentrations were recorded. Ketoacidosis was confirmed by the identification of acetone and the diagnosis of alcoholic ketoacidosis made on the basis of the history, autopsy findings and toxicological analysis.

Results

Twenty-three cases were identified where there was a diagnosis of alcoholic ketoacidosis. One additional case was added to the series where death was due to consumption of isopropanol. All had a history of alcohol abuse and none had a history of diabetes mellitus. None showed any evidence of starvation. In each of the cases the renal pathology was reviewed for the presence of the Armanni–Ebstein lesion and changes of diabetes nephropathy. Of the 23 cases, 11 had microscopic features of Armanni–Ebstein lesion (Fig. 1). Fat stains demonstrated the presence of fat in the vacuoles (Fig. 2). Even where a degree of autolysis was present, both the vacuoles and the presence of fat could be identified. None showed any changes of diabetic nephropathy. The liver showed fatty change in each case.

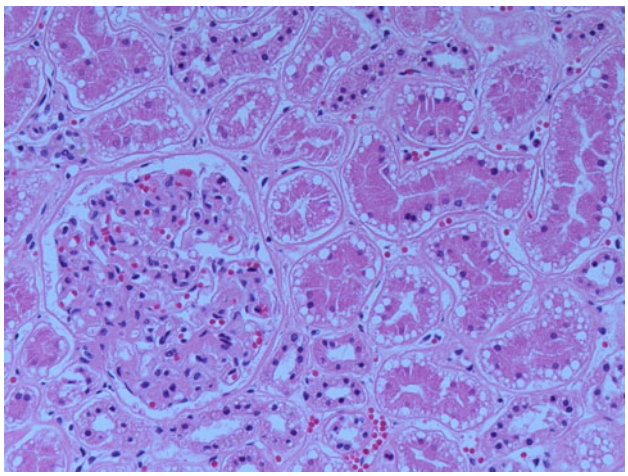

Fig. 1 Armanni–Ebstein lesion with subnuclear vacuolation of the proximal tubules

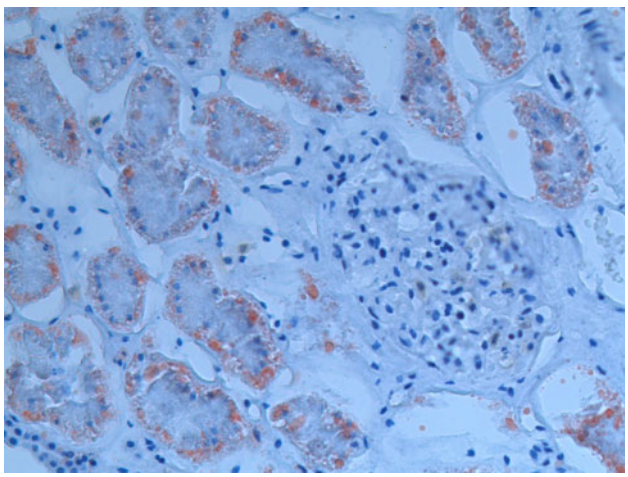

Fig. 2 Fat stain (oil red O) showing fat in the subnuclear vacuolations

The toxicology in each case is summarized in Table 1. The acetone concentrations ranged between 3 and 67 mg/100 mL (mean 17.9 mg/100 mL and median value of 16 mg/100 mL). In one chronic alcoholic reviewed without evidence of alcoholic ketoacidosis (negative acetone) the Armanni–Ebstein lesion was identified. In one case death was due to isopropanol poisoning. The decedent was a non-diabetic alcoholic and admitted to drinking isopropanol. His last admission to hospital was 4 days before his death and he left hospital the next day. He was found dead at home. At autopsy there was evidence of autolysis of the kidneys on histology, but the Armanni–Ebstein lesion was present on histology (Fig. 3). He had a fatty liver. His isopropanol concentration was 200 mg/100 mL and the acetone concentration was 232 mg/100 mL. Ethanol was negative. His glucose level on his last admission to hospital was normal (6.0 mmol/L) and his blood ethanol was negative as well.

Table 1 Acetone, ethanol and isoproponol concentrations in cases of alcoholic ketoacidosis with the Armanni–Ebstein lesion

Case	Age/ sex	Acetone mg/100 ml	Ethanol mg/100 ml	Isopropanol mg/100 ml
1	52 F	3 mg	–	–
2	69 M	13	45	8
3	61 M	25	19	–
4	42 F	67	–	6
5	42 F	17	–	3
6	43 F	16	276	12
7	54 M	15	–	–
8	59 M	16	23	15
9	57 M	13	124	10
10	34 F	9	–	–
11	51 M	3	–	–

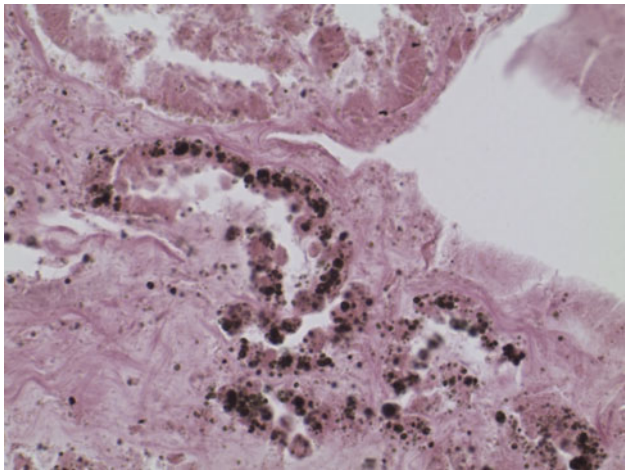

Fig. 3 Fat stain (osmium tetroxide) showing fat in the proximal renal tubules in isopropanol poisoning

Discussion

Sudden death in the alcoholic is a well recognized scenario for anyone performing a medico-legal autopsy. These cases may present a number of difficulties, as the history is often limited or incoherent, especially when the witnesses are themselves chronic alcoholics. These deaths often have no specific anatomical cause found. There are well recognized changes in alcohol abuse, the paradigmatic changes being in the liver with alcoholic steatosis and cirrhosis of the liver, but these are pointers to chronic alcohol abuse rather than being specific causes of death. A number of mechanisms may play a role in the death of a chronic alcoholic, including cardiac arrhythmias and biochemical imbalance that are not measurable, or not easily measurable at autopsy. One increasingly recognized cause of death is alcoholic ketacidodisis [9–12, 14].

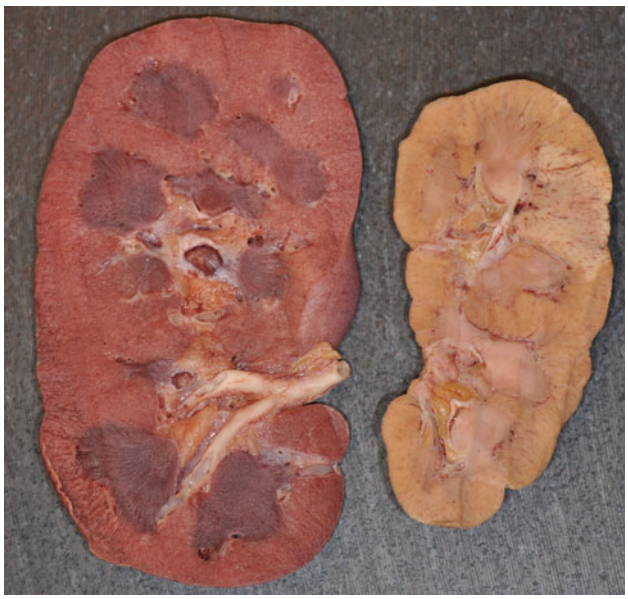

Fig. 4 Macroscopic appearance of the kidney in Alcoholic ketoacidosis on the *right* with normal kidney on the *left*

The Armanni–Ebstein lesion is a lesion seen in the renal tubules named after Armanni who described the appearance in 1877 and by Ebstein in 1882 [1]. It has been highly associated with diabetic coma. What constituents the vacuoles contain has been the subject of a number of studies. Richie and Waugh in 1957 described the lesion in 5 cases of diabetes mellitus as consisting of marked glycogenic vacuolization of the epithelium of renal tubules in the outer medulla [2] and innermost cortex with tubules in the central and outer cortex not affected. Subsequently Kock and Vestergaard reported the finding of the Armanni–Ebstein lesion in eight insulin dependent diabetics [3]. The deaths were attributable to diabetic ketoacidosis and they concluded that the Armanni–Ebstein lesion was strongly associated with death in diabetic coma. Neilson, Thomsen and colleagues further examined these lesions and reported that the vacuoles contained fat [4, 5]. In 2010 Byard also recorded fat in the lesions and pointed out that a clue to the diagnosis is the macroscopic appearance of the cortex with pallor present [15]. The same appearance may be seen in cases of alcoholic ketoacidosis (Fig. 4).

Miroy and Parai reported the case of a young non-diabetic child with the Armanni–Ebstein lesion who died of starvation [6]. There was biochemically confirmed ketoacidosis. Furthermore, hypothermia has been associated with Armanni–Ebstein lesion [16].

The case of Armanni–Ebstein lesion in isopropanol poisoning is interesting. Isopropanol is converted in the body to acetone and the clinical hallmark of isopropanol ingestion is a recorded isopropanol and acetone concentration without significant metabolic acidosis [17]. This

raises the question of whether the Armanni–Ebstein lesion is caused by ketosis rather than ketoacidosis.

Based on the observations in this series and the published data it seems reasonable to conclude that the Armanni–Ebstein lesion is a subnuclear vacuolation of proximal renal tubules associated with ketoacidosis and is not specific for diabetic ketoacidosis. A compounding factor is that these conditions may overlap, as pointed out by Zhou and Byard in their series of cases of Armanni–Ebstein lesion in hypothermia, where a number of the cases occurred amongst diabetics [16]. Where diabetes mellitus is suspected at autopsy, or where the Armanni–Ebstein lesion is seen in the absence of an appropriate history, vitreous glucose maybe measured. Another analysis to exclude diabetes is the examination of haemoglobin for HA1C, which is elevated in diabetes mellitus and can be measured at autopsy [18, 19]. Studies have indicated that glucose levels are usually normal in alcoholic ketoacidosis, but may be mildly elevated or subnormal [20].

In conclusion, there is expanding evidence that the Armanni–Ebstein lesion is a marker of ketoacidosis that is not limited to diabetics. The case of isopropanol poisoning with Armanni–Ebstein lesion raises the question of whether it is ketosis, rather than ketoacidosis that is required to produce the lesion.

Key points

1. Armanni–Ebstein lesion, is sub-nuclear vacuolation of the renal tubules traditionally associated with deaths from diabetic ketoacidosis.
2. Armanni–Ebstein lesion has been shown to contain fat.
3. Armanni–Ebstein lesion may be seen in alcoholic ketoacidosis.
4. The kidneys with Armanni–Ebstein lesion may appear pale macroscopically.
5. Armanni–Ebstein lesion is not specific for diabetic ketoacidosis

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