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B. Brinkmann · G. Fechner · B. Karger · A. DuChesne

Ketoacidosis and lactic acidosis – frequent causes of death in chronic alcoholics?

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Abstract In clinical medicine, severe keto- or lactic adicosis associated with vomiting, nausea, abdominal pain, tachycardia or pathological respiration, has been described in chronic alcoholics. This study reports on fatalities of chronic alcoholics where the cause of death could not be determined by thorough autopsy, histology and toxicology including determination of alcohol concentration. In a first series, acetone was determined in the blood of such chronic alcoholics (n = 24), diabetics with metabolic decompensation (n = 7), cases of hypothermia (n = 7) and controls (n = 218). Among the 24 chronic alcoholics where the cause of death was unknown, 9 cases showed very high levels of acetone (74–400 mg/l). These comprised 6 cases without additional findings and 3 cases where a second patho-mechanism such as intoxication possibly contributed to the cause of death. In a second series, the sum values according to Traub (lactate/glucose) were determined in cerebrospinal liquor of chronic alcoholics with undetermined cause of death (n = 45), diabetics (n = 6) and controls (n = 39). Among the 45 alcoholics, 17 cases showed very high sum values (294–594 mg/dl) including 8 cases where non-lethal intoxications may have contributed to the final outcome. Other causes of a ketoacidosis or lactic acidosis (e.g. diabetes) were excluded in both groups of alcoholics. Consequently, ketoacidosis and lactic acidosis can be the cause of death of chronic alcoholics in a considerable number of cases where no pathomorphological or toxicological changes are present. A scheme for medical and laboratory examination is described.

Key words Metabolic acidosis · Ketoacidosis · Lactic acidosis · Cause of death · Chronic alcoholism

B. Brinkmann (✉) · G. Fechner · B. Karger · A. DuChesne
Institut für Rechtsmedizin, Westfälische Wilhelms-Universität, von-Esmarch-Strasse 62, D-48129 Munster, Germany
Fax: +49 (251) 8355 158; e-mail: brinkma@uni-meunster.de

Introduction

In cases of sudden unexpected death, the cause of death remains uncertain in 1–3% even if a thorough post-mortem including comprehensive histological, toxicological and microbiological investigations is performed (Janssen and Naeve 1975). This percentage rises significantly to 5–10% in chronic alcoholics (Clark 1988; Hanssen and Simonsen 1991) even if detailed morphometric investigations are carried out (e.g. Ahmed et al. 1996). An increasing number of clinical reports dealing with life threatening metabolic disorders in chronic alcoholics that relate either to ketoacidosis or to lactic acidosis have been published (e.g. Duffens and Marx 1987; Habscheid and Heidbreder 1988; Koch 1993). In this study, deaths of chronic alcoholics were investigated with regard to these metabolic disorders. Control groups as well as fatalities from hypothermia and diabetes, which show similar metabolic dysregulations, were also investigated.

Materials and methods

Two metabolic decompensations of chronic alcoholics, i. e. (1) AKA (alcoholic keto acidosis) and (2) ALA (alcoholic lactic acidosis) were studied separately in two autopsy series. The object of this investigation was a subgroup of sudden unexpected deaths where the previous history and/or morphology showed strong indication of chronic alcoholism but where the post-mortem including histomorphology and complete toxicology (legal and illegal drugs including alcohol, toxins) failed to explain the cause of death.

AKA (alcoholic keto acidosis). Under this aspect the following fatalities were investigated.
- Alcoholics (n = 24) where the cause of death could not be determined.
- Diabetics (n = 7) with metabolic findings relating to the cause of death.
- Controls (n = 218) with defined causes of death such as trauma or various natural deaths with acute findings.
- Cases with evidence of hypothermia (n = 7).

ALA (alcoholic lactic acidosis). Under this aspect 3 subgroups were investigated:
- Alcoholics (n = 45) where the cause of death could not be determined

– Diabetics (n = 6) with metabolic findings relating to the cause of death
– Controls (n = 39) with defined causes of death such as trauma or various natural deaths.

Autopsy and complete histopathology was performed in all cases in both series including the controls. Furthermore, an extensive toxicological analysis in blood, urine, liver and stomach content for a broad spectrum of drugs including alcohol and toxins was performed in all cases where the cause of death could not be determined precisely. Cases indicative of chronic alcohol consumption and diabetes were investigated for these disorders. This included HbA1, related histopathology (kidneys, liver, pancreas) and gross anatomy (e. g. xantosis). Also, cerebrospinal fluid was investigated for sugars and the sum values were determined additionally in vitreous body and in pericardial serum in selected cases.

Analyses

– Determination of glucose and lactate by enzyme tests (Hitachi 747, Hitachi 717).
– Free acetone by head space gas chromatography (flame ionisation detector; GCF45, Perkin-Elmer).
– Haemoglobin A1 by HPL-chromatography (Merck).

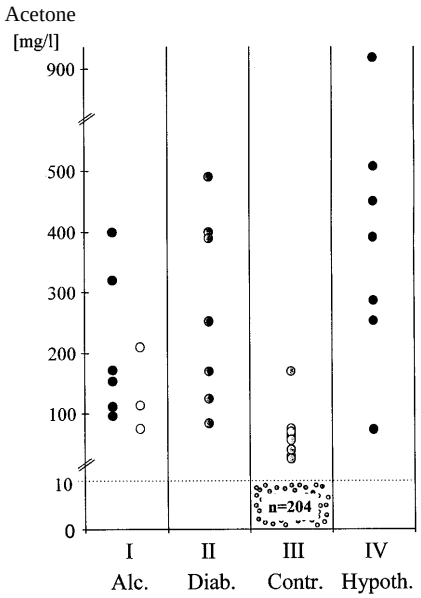

Fig. 1 Levels of free acetone in blood (mg/l). I – chronic alcoholics (n = 9) without a clearly defined cause of death, full circles: no contributing factors, empty circles: contributing factors. II – diabetics (n = 7). III – non-diabetics (n = 218) with a clearly defined cause of death. 204 of these cases remained below 10 mg/l (cut-off level). IV – cases of hypothermia (n = 7)

Results

1 AKA

– Alcoholics. Out of 24 chronic alcoholics lacking a clearly defined cause of death after thorough investigations, 9 cases showed markedly elevated levels of acetone from 74 to 400 mg/l with a mean value of 183 mg/l (Fig. 1). Among these, two subgroups can be differentiated (Table 1): Six cases showed pathological levels of acetone only (with little alcohol in one of them). In 3 cases additional pathomechanisms contributed to the cause of death. HBA1 was always below 5.6% and in no case did histopathology show signs for diabetes. In the remaining 15 cases, acetone was below 10 mg/l in 13 cases and values of 40 mg/l and 66 mg/l were measured in two cases.

– Diabetics. Acetone levels ranged between 84 and 490 mg/l (mean value: 275 mg/l) (Fig. 1). The HbA1 values ranged between 5% and 13%. Histopathology revealed related changes such as diabetic glomerulosclerosis or Armanni-Ebstein cells in all 7 cases.

– Hypothermia. The level of free acetone ranged between 75 and 925 mg/l (mean value: 410 mg/l) (Fig. 1). HbA1 was always below 5.6%. Histopathology showed no indication of diabetes.

– Controls. The acetone level was below 10 mg/l (cut-off level) in 204 cases (Fig. 1). Thirteen cases showed values between 10 and 75 mg/l and one single case 170 mg/l. This highest level was measured in a psychiatric patient found dead in a forest after being absent for several days, which indicates the possibility of severe food shortage.

2 ALA

– Alcoholics. Out of 45 chronic alcoholics lacking a clearly defined cause of death after thorough investigations, 17 cases showed very high sum values ranging from 294 to 594 mg/dl (mean value: 402 mg/dl) (Fig. 2). Again, two subgroups can be differentiated with regard to additional pathomechanisms such as high blood alcohol concentrations or illicit drugs contributing to the cause of death (Table 2). Histopathology gave no indi-

Table 1 Ketoacidosis in chronic alcoholics

No.	Age/sex	Pm-interval days	Acetone mg/l	BAC ‰	UAC ‰	Special features
1	64/f	4	112	0	0	
2	55/f	2	96	0	0	
3	61/f	5	172	0.3	0.8	
4	44/f	2	154	0	0	
5	33/m	4	320	0	0	
6	57/f	8	400	0	–	Traces of 2-propanol s.v. lactate/glucose 294
7	36/f	2	114	0	0.78	Barbiturates
8	60/m	2	74	0	0	Anaemia due to bleeding
9	41/f	1	210	2.7	3.0	Alcoholic intoxication

f = female, *m* = male, *pm* = post mortem, *BAC* = blood alcohol concentration, *UAC* = urine alcohol concentration; *italic letters* = cases with combined mechanisms

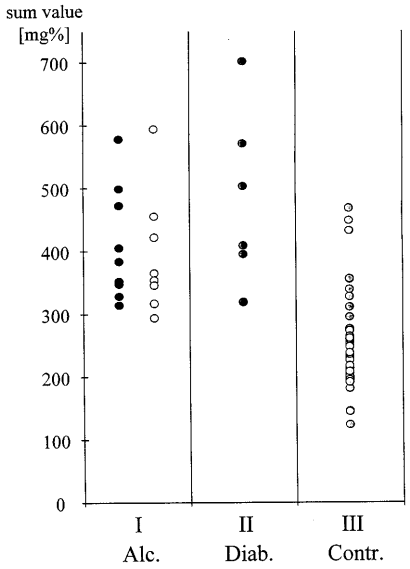

Fig. 2 Sum values of lactate/glucose (Traub) in cerebrospinal liquor (mg/dl). I – chronic alcoholics (n = 17) without a clearly defined cause of death, full circles: no contributing factors, empty circles: contributing factors. II – diabetics (n = 6). III – non-diabetics (n = 39) with a clearly defined cause of death

cation of diabetes and HBA1 was below 5.6% in all cases. In the remaining 28 cases, the sum values varied between 175 mg/dl and 268 mg/dl.

– Diabetics. The high sum values varying from 319 to 702 mg/dl (mean value: 370 mg/dl) (Fig. 2) were to be expected. The HbA1 values ranged between 5.8% and 16%. Histopathology showed related changes in all cases.

– Controls. Sum values between 124 and 468 mg/dl (mean value: 250 mg/dl) were determined in this group (Fig. 2). Eight cases showed sum values higher than 300 mg/dl. These were cases of protracted agony or showed hyperglycaemia due to cerebral damages such as a metastatic tumor or carbon monoxide intoxication.

The sum values were also determined in the vitreous body and pericardial serum. In nine cases of ALA the sum values in the vitreous body varied between 215 and 598 mg/dl (mean: 349 mg/dl) and in the controls (n = 23) between 91–275 mg/dl (mean 169 mg/dl). The sum values of pericardial serum in cases of ALA varied between 457 and 918 mg/dl (n = 13, mean: 621 mg/dl) and in the controls (n = 25) between 192 and 739 mg/dl (mean: 397 mg/dl).

Correlation of the post mortem interval with the acetone and the sum values (Bravais-test) showed a non-significant test result for the sum values (correlation coefficient r = 0.25 significance value) and a weak correlation for the acetone values. However, if case 6 (Table 1) with a post mortem interval of 8 days is excluded, the result is non-significant (r = 0.30 significance value) for acetone, as well.

Discussion

Metabolic acidosis is known to occur in association with diabetes, periods of hunger, shock syndromes, hypothermia and chronic alcoholism. Biochemically, ketoacidosis and lactic acidosis can be differentiated. Dillon and coworkers (1940) were the first to describe severe metabolic acidosis in seven non-diabetic chronic alcoholics. The term ‘alcoholic ketoacidosis’ (AKA) was not introduced until 1971 (Jenkins et al. 1971). ‘Alcoholic lactic acidosis’ (ALA) is caused by thiamine deficiency and was defined later (Thirunavakkarasu 1979; Hoyumpa 1980; Campbell 1984). Doehn and Schwartau (1982) empha-

Table 2 Lactacidosis in chronic alcoholics

No.	Age/sex	Pm-interval days	Sum value glucose/lactate liquor	BAC ‰	UAC ‰	Special features
1	63/m	2	328	1.0		
2	28/m	1	472	0	0	
3	35/m	3	578	0.6		
4	56/f	3	499	0	0	
5	56/f	1	405	0	0.6	
6	53/m	1	384	0.6	1.7	
7	44/m	1	348	0	0	
8	56/m	2	352	0.5	0.5	
9	61/m	2	314	0	0	
10	33/m	3	365	1.1	1.9	Narcotics
11	30/m	2	594	0	0	Narcotics
12	32/m	2	317	2.2	2.8	Narcotics/alcohol
13	28/m	4	455	1.0	1.0	Narcotics/alcohol
14	35/m	2	422	2.8	4.7	Alcohol
15	36/f	1	354	3.4		Alcohol
16	49/m	2	346	3.0	3.7	Alcohol
17	30/m		294	0		Narcotics

f = female, *m* = male, *pm* = post mortem, *BAC* = blood alcohol concentration, *UAC* = urine alcohol concentration; *italic letters* = cases with combined mechanisms

sized that ALA can be the cause of sudden death in alcoholics. Five typical symptoms have been described in both forms, i. e. vomiting, nausea, abdominal pains, tachycardia, and the Kussmaul form of respiration. The syndrome typically starts when alcoholic excess is followed by a considerable period of fasting or is associated with concurrent disease. A decreasing level of consciousness and also abstention from further alcohol consumption is commonly present before coma. A decisive laboratory finding is metabolic acidosis in combination with a gap of anions. Differential diagnoses are coma diabeticum, coma uraemicum and several intoxications such as from ethylene glycol, methanol, isopropanol and salicylates (Halperin et al. 1983; Campbell 1984; Thompson et al. 1986; Madeya et al. 1991; Caspar et al. 1993; Koch 1993). Additional triggering factors for the occurrence of AKA and ALA can be fasting, repeated vomiting and insulin deficiency due to alcoholic pancreatitis (Caspar et al.1993; Koch 1993).

Alcoholic ketoacidosis (AKA). Increased alcohol consumption leads to an increase of the NADH/NAD+ ratio which in turn inhibits gluconeogenesis and the utilisation of free fatty acids. Also, fasting induced carbohydrate deficiency with subsequent glycogen depletion and decreased gluconeogenesis with decreased insulin liberation induce increased lipolysis with subsequent increase of keto bodies. If dehydration due to vomiting occurs, renal failure can in addition lead to a retention of keto bodies (Caspar et al. 1993). The blood level of acetone is considered to be a parameter for the severity of AKA. Normal values in the serum of living persons range from 2.3 to 3.5 mg/l (Geigy-tables). In deaths due to diabetic coma the acetone levels reported range from 16 to 846 mg/l with most values between 300 and 400 mg/l (Osterhaus 1968; Kernbach et al. 1983). Nondiabetic controls showed values below 10 mg/l (Osterhaus 1968) or even below 5 mg/l (Friedrich 1986). The high autolytic resistance of acetone (Osterhaus 1968; Kugler and Oehmichen 1986) is corroborated by the low acetone levels determined in the vast majority of the control group (10 mg/l) and by the non-significant correlation test result in the early post-mortem period. This indicates the absence of a relevant increase of the acetone level during the first five days after death.

In this series, 9 cases out of 24 chronic alcoholics showed very high acetone levels (Table 1). In three of these 9 cases, additional pathomechanisms likely contributed to the cause of death including the case with the lowest acetone level (74 mg/l), where anaemia due to bleeding was also effective (Table 1). Also, non-lethal intoxications from barbiturates or alcohol can be combined with very high acetone levels (Table 1). The acetone levels measured in the fatalities from diabetes and hypothermia were also very high. Metabolic ketoacidosis is well known in diabetics but has also been reported in cases of hypothermia (e.g. Hanson and Johnson 1966). Another rare cause of increased acetone can be isopropanol poisoning. This substance is rapidly oxidised to acetone. Increased acetone can persist for several days while isopropanol will disappear much earlier (Petkovits et al. 1989). This possible interference must be investigated by especially considering the previous history and the possible occurrence of isopropanol as a congener of alcoholic beverages. In this series, traces of isopropanol were detectable in one case only (Table 1).

These results show that acetone values higher than approximately 90 mg/l can indicate a fatal ketoacidotic coma. So if the cause of death cannot be explained by morphological and toxicological methods or blood alcohol concentration, AKA with high acetone values above this threshold can constitute the cause of death in chronic alcoholics.

In the present investigation, determination of free acetone was carried out. However, β-hydroxybutyric acid might be a better indicator because there is a closer association to the increase of the $NADH/NAD^+$ ratio and β-hydroxybutyric acid comprises two thirds of all keto bodies in healthy persons. For this reason the determination of β-hydroxybutyric acid has meanwhile been recommended as a possibly more suitable indicator of AKA (Caspar et al.1993; Iten et al.1996).

Alcoholic lactic acidosis (ALA). ALA is caused by an elevation of the NADH/NAD+ ratio with increased formation of lactate from pyruvate, diminished gluconeogenesis and decreased lactate uptake into the liver (Duffens and Marx 1987; Fulop 1989; Koch 1993). Thiamine deficiency due to malnutrition and the direct action of alcohol are held responsible for the occurrence of ALA (Hoyumpa 1980; Weitbrecht 1984). Thiamine is known to act as a coenzyme during the breakdown of pyruvate to acetyl-CoA. In thiamine deficiency, pyruvate is reduced to lactate. In alcoholics, other complications can also act as triggers for lactic acidosis, e.g. haemorrhagic shock, circulatory depression in the intestine or severe hypothermia (Fulop 1989; Habscheid and Heidbreder 1988). Since glucose in blood and liquor is converted into lactate during the postmortem period, the establishment of the sum value (Traub 1969) is necessary for the investigation of fatalities.

Our cases (Table 2) were considered fatal ALA in alcoholics only if the following criteria were met: (1) liquor sum values (Traub) above 300 mg/dl, (2) no indication of diabetes from previous history, histology or HbA1 determinations, (3) no cause of death found even after extensive toxicology. The sum values in liquor ranged between 294 and 594 mg/dl (mean value: 402 mg/dl) in 17 cases. In 8 of these, there were additional findings which possibly contributed to the cause of death but the sum values did not markedly differ from those without additional findings (Table 2). The minimum value of 300 mg/dl in this study discriminates between lactic acidosis and the controls of non-diabetic deaths in the majority of cases (22/29). But since the sum values of the cases considered to be fatal ALA showed no large difference to the control group or to the remaining alcoholics, the minimum value of 300 mg/dl can only be regarded an indication of ALA and has to be interpreted cautiously. Since the high liquor sum values represented the only significant finding after thorough investigations in 17 out of 45 alcoholics, we assume a fatal lactic acidosis to be the cause of death in

these cases. Kernbach et al. (1983) and Oehmichen and Kugler (1985) established threshold values of 360 and 500 mg/dl, respectively, for diabetic deaths. Consequently, a threshold value of approximately 400 mg/dl appears to be appropriate for a reliable diagnosis of fatal ALA although our results indicate that death can also occur with lower values.

The sum values in the vitreous body and pericardial serum measured indicate that discrimination can be accomplished best in the cerebrospinal liquor, which has been described as a fluid protected well in the postmortem period (Kernbach et al. 1983). The non-significant correlation test result for the sum values and the length of the post-mortem period indicates that the sum value does not markedly change during the first 4 days after death. Since the investigations for AKA and ALA were performed separately, both acetone and the sum value were determined simultaneously in only one case (Table 1). This showed an increased blood level of acetone (400 mg/l) as well as a high sum value of glucose/lactate (294 mg/dl). So a combination of AKA and ALA seems possible. This combination could lead to a fatal metabolic breakdown even if only intermediate elevations of these substances occur.

Finally, we conclude that keto- and lactic acidosis can be the cause of sudden deaths of alcoholics either in isolation or in combination, which suggests that an investigation for both metabolic decompensations represents the most promising approach. Triggers or concurrent mechanisms such as hypothermia or additional drug findings are possible but do not represent prerequisites.

In order to detect fatal cases of AKA and ALA we recommend the following procedure and sampling scheme:

(1) careful evaluation of anamnestic data: chronic alcoholism, fasting, abstention from alcohol and symptoms of a severe disease one or two days before death,
(2) performance of preliminary tests for glucose and acetone in cerebrospinal liquor during autopsy,
(3) exclusion of diabetes and other causes of metabolic acidosis; histopathologic characteristics of chronic alcoholism,
(4) collection of blood and liquor during autopsy for the determination of

– the “sum value” glucose/lactate in cerebrospinal liquor (critical value > 300–400 mg/dl)

– acetone in blood (critical value > 90 mg/l) or β-hydroxybutyric acid (Caspar et al. 1993: critical value > 4 mmol/l)

– HbA1 in blood (6%)

(5) exclusion of intoxications as the cause of metabolic acidosis.

References

Ahmad ANH, Elton RA, Busuttil A (1996) Assessment of myocardial vasculature in chronic alcoholics without established cardiomyopathy. Int J Legal Med 109:167–172

Campbell CH (1984) The severe lactic acidosis of thiamine deficiency: Acute pernicious or fulminating beriberi. Lancet 2(8400): 446–449

Caspar CB, Risti B, Iten PX, Jost R. Russi EW, Speich R (1993) Alkoholische Ketoacidose. Schweiz Med Wochenschr 123: 1929–1934

Ciba-tables (1996), Basel

Clark JC (1988) Sudden death in the chronic alcoholic. Forensic Sci Int 36:105–111

Denmark LN (1993) The investigation of beta-hydroxybutyrate as a marker for sudden death due to hypog!ycaemia in alcoholics. Forensic Sci Int 62:225–232

Dillon ES, Dyer WW, Smelo LS (1940) Ketone acidosis in nondiabetic adults. Med Clin North Am 24:1823–1822

Doehn M, Schwartau M (1982) Alkoholinduzierte Lactacidose bei Thiaminmangel. Z Rechtsmed 89:125–130

Duffens K, Marx JA (1987) Alcoholic ketoacidosis – a review. J Emerg Med 5:399–406

Friedrich G (1986) Forensische postmortale Biochemie. In: Forster B. Praxis der Rechtsmedizin. Thieme, Stuttgart New York

Fulop M (1989) Alcoholism, ketoacidosis, and lactic acidosis. Diabet Metab Rev 5:365–378

Habscheid W, Heidbreder E (1988) Letaler Verlauf einer alkoholinduzierten Ketoacidose. Dtsch Med Wschr 113:2007–2009

Halperin ML, Hammeke M, Josse RG, Jungas RL (1983) Metabolic acidosis in the alcoholic: A pathophysiologic approach. Metabolism 32:308–314

Hansen AU, Simonsen J (1991) The manner and cause of death in a forensic series of chronic alcoholism. Forensic Sci Int 49: 171–178

Hanson PG, Johnson RE (1966) Variation of plasma ketones and free fatty acids during acute cold exposure in man. J Appl Physiol 20:56–61

Hoyumpa AM (1980) Mechanism of thiamin deficiency in chronic alcoholism. Am J Clin Nutr 33:2750–2761

Iten PX, Meier M, Bär W (1996) β-Hydroxybuttersäure, ein Indikator für eine alkoholische Ketoacidose als Todesursache bei unerwartet verstorbenen Alkoholikern. 75. DGRM-Jahrestagung. Zürich

Janssen W. Naeve W (1975) Der plötzliche Tod aus natürlicher Ursache. In: Mueller B. Gerichtliche Medizin. Springer, Berlin Heidelberg New York

Jenkins DW, Eckel RE, Craig JW (1971) Alcoholic ketoacidosis. J Am Med Assn 217:177–183

Kernbach G, Koops E, Brinkmann B (1983) Biochemische Parameter bei 31 tödlichen diabetischen Stoffwechselentgleisungen.Beitr ger Med 42:301–306

Koch HU (1993) Die akute alkohol-induzierte Azidose. Medwelt 44:623–626

Kugler J, Oehmichen M (1986) Untersuchungen zum Glucosestoffwechsel an der Leiche. Beitr Ger Med 44:185–188

Madeya S, Labenz J, Börsch G (1991)Alkoholinduzierte Ketoacidose. Folge 1: Erscheinungsbild, Diagnose, Differentialdiagnose. Fortschr Med 109:465–466,,-

Madeya S, Labenz J, Börsch G (1991) Alkoholinduzierte Ketoacidose. Folge 2: Therapie, Verlauf und pathogenetische Theorien. Fortsch Med 109:480–481

Osterhaus R (1968) Untersuchungen über Ketonkörperkonzentationen im Sektionsgut. Beitr Ger Med 25:330–332

Petkovits T, Bohn G, Brinkmann B (1989) Rechtsmedizinische und toxikologische Aspekte bei Propanol-2-Intoxikationen. Z Rechtsmed 102:69–75

Thirunavukkarasu K (1979) Treatment of alcoholic lactic acidosis. Med J Aust 583–584

Thompson CJ, Johnston DG, Baylis PH, Anderson J (1986) Alcoholic ketoacidosis: an underdiagnosed condition? Brit Med J 292:463–465

Traub F (1969) Methode zur Erkennung von tödlichen Zuckerstoffwechselstörungen an der Leiche (Diabetes mellitus und Hypoglykämie). Zbl Allg Path 112:390–399

Weitbrecht WU (1984) Vitamin-B-Mangel und Alkoholismus. Therapiewoche 34:3264–3270