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Massive lactic- and keto- acidosis with glucagon deficiency in a chronic alcoholic patient

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Abbreviations:

BMI: Body mass index

GH: Growth hormone

IGF1: Insulin-like growth factor-1

NAD: Nicotinamide dinucleotide

SHBG: Sex hormone-binding globulin

A non-diabetic, chronic alcoholic and undernourished patient (BMI= 16.6 kg/m²) was admitted to the emergency department of the hospital. He had fasted for the previous three days. His blood lactate and ketone body concentrations were massively elevated (respectively, 18 mmol/L and 14 mmol/L). Ethanolemia was negative. Massive metabolic acidosis was noted with a pH of 7.04. Renal function remained normal. There was mild hepatocellular deficiency but no acute pancreatitis. The patient was hypoglycemic at admission with a blood glucose level of 3.0 mmol/L and low insulin, C-peptide, and insulin-like growth factor-1 (IGF1) concentrations, as well as a very low glucagon concentrations (5.2 ng/L, N: 8-74 ng/L) for the prevailing glycemia. By contrast, cortisol, sex hormone-binding globulin (SHBG), and growth hormone (GH) concentrations were elevated. In the intensive care unit, he received a saline solution of dextrose, thiamine, pyridoxine, folic acid and nicotinamide. Progressive normalization of blood glucose was associated with increases in insulin and C-peptide and a decrease of urinary cortisol, circulating GH and SHBG but no change of plasma glucagon. His biological markers normalized by day 2 and he left the hospital on day 5. The patient was re-examined in hospital 7 months later for his thiamine status and a liquid meal test was performed (Delical HP-HC Lactalis, 4 mL/kg) for the glucagon secretion response. His total thiamine concentration before the meal was 118 nmol/L indicating a deficiency. Basal blood glucose was 6.5 mmol/L and increased modestly during the meal together with a normal insulin secretion. Basal glucagon remained very low (7.4 ng/mL) and raised to only 15.8 ng/mL 2 hours after the meal. These data are summarized in Table 1.

Alcohol metabolism in the liver induces massive formation of NADH, H⁺ and acetyl-CoA leading to lactate and ketone body overflow. However, no alcohol was detected in the blood and severe lactic acidosis is uncommon in alcoholic patients [1] as well as the association of lactic acidosis and ketoacidosis [1,2].

A liver failure could have accounted for the unusually high lactate concentrations since the liver normally takes up blood lactate for gluconeogenesis. However, there was no major hepatocellular deficiency since proteinemia, prothrombin time, and activated partial thromboplastin time (APTT) were normal. Nevertheless, his blood glucose was lower than that seen in undernourished patients with a low BMI [3] or in starved human subjects [4], suggesting a reduced capacity for glucose synthesis which might have contributed to the elevated lactate concentration. Finally, thiamine (vitamin B1) deficiency due to chronic malnutrition might be also a contributing factor. Thiamine pyrophosphate is an obligatory cofactor of a number of enzymes and the lack of thiamine has major metabolic consequences since (i) pyruvate cannot be used as an energy substrate by the liver or by other oxidative tissues and can yield lactate and (ii) acetyl-CoA coming from fatty acids will be preferentially oriented in the liver towards ketone body synthesis rather than to the Krebs cycle.

The ketone body levels seen in this patient were higher than those observed after long-term starvation in humans [3]. One important factor in this case was the marked hypoglycemia. It may have contributed to the low insulin level, favoring massive lipolysis in adipose tissue and high concentrations of plasma fatty acids, as observed. The high levels of cortisol and GH probably also contributed to this situation. Thus, acute starvation and chronic malnutrition were certainly crucial etiologic factors.

A puzzling feature is the low basal plasma glucagon concentration (even 7 months after recovery). This low glucagon by reducing the gluconeogenic capacity can contribute to the hypoglycemia and to the high lactate concentration. Interestingly, despite the low glucagon concentration, ketone body levels were very high suggesting that, in humans, if glucagon is necessary to maintain glucose homeostasis, it is not required for ketone body synthesis in conditions of low insulin [5]. The reasons for the glucagon deficiency in this patient are

unclear. There was no sign of acute or chronic pancreatitis. An inherent defect in glucagon synthesis, maturation or secretion in this patient cannot be dismissed.

In conclusion, the extreme metabolic situation of this patient was a consequence of alcohol abuse inducing mild liver dysfunction, malnutrition, starvation and thiamine deficiency associated to a defect in glucagon production.

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INFORMED CONSENT

An informed consent was obtained from the patient.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in relation with this work.

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Table 1. Laboratory results and test meal

Blood parameters			Patient value							Reference values
pH			7.04							7.35-7.45
PaCO ₂	(mmHg)		10							35-45
PaO ₂	(mmHg)		138							> 80
SatO ₂	(%)		97.4							95-99
Bicarbonate	(mmol/L)		3							23-31
Lactate	(mmol/L)		18							0.4-1.5
Ketone bodies	(mmol/L)		14							< 0.6
Fasting glycemia	(mmol/L)		3.0							4.1-5.9
Urea	(mmol/L)		5.5							3-7
Creatinine	(mmol/L)		90							45-97
AST	(U/L)		208							< 35
ALT	(U/L)		87							< 43
γGT	(U/L)		491							< 45
Alkaline phosphatases	(U/L)		144							< 115
Total bilirubin	(□mol/L)		24							< 17
Lipase	(U/L)		21							4-30
Protein	(g/L)		76							60-84
Prothrombin time	(%)		77							> 70
APTT	(patient/control)		0.92							0.80-1.20
Ethanolemia	(g/L)		< 0.10							< 0.10
Salicylate	(mg/L)		undetectable							negative
Methanol	(g/L)		undetectable							negative
Ethylene glycol	(g/L)		undetectable							negative
Time in emergency	(hours)	0	3	8	10	24	48	72	Reference values	
Blood parameters										
Lactate	(mmol/L)	18	10.2	2.8	n.d.	2.2	n.d.	1.2	0.4-1.5	
Glucose	(mmol/L)	3.0	4.47	12.55	14.15	8.27	5.3	7.17	4.1-5.9	
Insulin	(mUI/L)	0.77	2.67	n.d.	8.21	12	3.71	5.88	2.7-23.5	
C-peptide	(nmol/L)	0.2	0.398	1.12	1.62	1.24	0.56	0.76	0.36-1.25	
Cortisol	(nmol/L)	1679	1653	955	660	401	339	339	145-475	
GH	(ng/ml)	2.8	1.93	1.37	0.73	0.55	1.13	0.57	< 6.6	
IGF1	(ng/ml)	29	27.8	30.3	31.4	36.4	31.2	37.6	46.5-192	
Glucagon	(ng/L)	5.2	5.2	5.2	5.2	5.2	5.2	5.2	8-74	
SHBG	(nmol/L)	107	88.7	81.8	79.2	69	66.9	70.9	11.75-47.05	
Free fatty acids	(mmol/L)	2.76	1.90	0.89	0.62	1.21	0.78	0.90	1.2-3.3 (24 h fasting)	
Test meal (minutes)	0	15	30	60	90	120				
Blood parameters										
Glucose (mmol/L)	6.15	8.05	7.7	6.27	6.44	5.36				
Insulin (mUI/L)	4.48	40.6	51.9	38.5	31.7	24.9				
C-peptide (nmol/L)	0.62	1.57	2.13	2.80	3.00	2.43				
Cortisol (nmol/L)	453	n.d.	n.d.	n.d.	n.d.	n.d.				
Glucagon (ng/L)	7.4	9.6	10.9	11.4	9.0	15.8				
Thiamine (nmol/L)	References									
- Not phosphorylated	0	0-8								
- Di-phosphorylated	117	120-230								
- Tri-phosphorylated	1	0-20								
- Total	118	126-250								