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Characteristics of Severe Alcoholic Ketoacidosis with a Reversible Visual Disturbance

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Abstract

Purpose: To clarify the characteristics of AKA patients with visual disturbances.

Material and methods: An Ichushi and Pubmed search was undertaken to identify articles that reported patients with visual disturbances due to AKA. The clinical data in the articles were reviewed. This study also performed a subanalysis by classifying the patients with visual disturbance due to AKA into two groups: an arrest group, which experienced cardiac arrest during hospitalization and a no-arrest group, which did not.

Results: There were 12 case reports describing patients with visual disturbances due to AKA. There were 14 patients who showed a visual disturbance due to AKA. There were 11 males and 3 females. The range of age was from 44 to 68, with an average of 55 years old. Seven cases had loss of consciousness and the systolic blood pressure of in 12 cases was under 90 mmHg. All cases show arterial blood gas pH under 6.90 and severe metabolic acidosis. All but one of the visual disturbance cases improved after correction of acidemia by infusion of sodium bicarbonate or blood purification. Six cases experienced cardiac arrest during their hospitalization. Three cases finally died. The subanalysis showed the average pH on arrival in the arrest group was lower than that in the no-arrest group (6.63 vs. 6.75, respectively). And the survival ratio in the arrest group was smaller than that in the no-arrest group (50 vs. 100%, respectively).

Conclusion: Severe AKA was associated with visual disturbances, which could be cured by correction of acidosis. In addition, patients with severe AKA with a pH on arterial gas analysis under 6.70 tended to experience cardiac arrest and the patients with arrest had a poor prognosis. Physicians should understand how to treat such patients.

Introduction

Alcoholic Ketoacidosis (AKA) is an acute metabolic acidosis that typically occurs in people who chronically abuse alcohol and have a recent history of binge drinking, little or no food intake and persistent vomiting [1]. AKA is a result of starvation with glycogen depletion and counter-regulatory hormone production, an increased ratio of Nicotinamide Adenine Dinucleotide (NADH) to Nicotinamide Adenine Dinucleotide (NAD+) related to the metabolism of ethanol, and volume depletion resulting in ketogenesis [1]. This results in a predominant increase of β-hydroxybutyrate and a high anion gap in contrast to the predominant increase of acetoacetate in diabetic ketoacidosis. A urine test strip for the diagnosis of ketonemia is for acetoacetate and acetone but not for β-hydroxybutyrate so that, AKA may be misdiagnosed by using this method. In addition, patients with a severe case of AKA cannot drink alcohol, so the value of alcohol may be zero on arrival. Accordingly, obtaining a history of alcohol consumption and measuring the level of β-hydroxybutyrate is important for patients with metabolic acidosis and a high anion gap to correctly diagnose AKA. The main symptoms of this condition are nausea, vomiting and/or abdominal pain [2]. These symptoms are usually improved by the infusion of 5% dextrose and thiamine. However, AKA is occasionally associated with multiple complications and treatment in such cases requires a multidisciplinary approach [3].

Patients that chronically abuse alcohol rarely show visual disturbances due to cerebral infarction, optic neuritis, or demyelination induced by deficiency of thiamine [4-6]. Severe AKA, it can cause visual disturbances [7-9]. However, no report has analyzed the characteristics of AKA with visual disturbances. Hence, the current study was a clinical analysis of previous reports describing AKA patients with visual disturbances.

Material and Methods

An Ichushi search (Japana Centra Revuo Medicine), which collected summaries of Japanese medical articles, was undertaken to identify articles from 1983 to 2011 using the key words "ethanol", "acidosis" and "visual" or "blindness" to find manuscripts that reported patients with visual disturbances due to AKA. A Pubmed search was also undertaken to identify articles from 1976 to 2011 using the same key words. Additional articles were identified by a manual search of the references from the key articles.

The reports were reviewed to determine the gender, age, the degree of alcohol abuse, consciousness, pupil diameter, light reflex, systolic blood pressure on arrival, the results of an arterial blood gas analysis, the levels of alcohol, β-hydroxybutyrate, acetoacetate, lactate and glucose, the incidence of cardiac arrest hospitalization, the need for intensive care, and the final outcome (survival or not).

This study also performed a sub-analysis classifying the patients with visual disturbances due to AKA into two groups: an arrest group,

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which experienced cardiac arrest during hospitalization and a no-arrest group, which did not. The gender, age, consciousness, pupil diameter, light reflex, systolic blood pressure on arrival, and results of arterial blood gas analysis were compared between the two groups.

Both the chi-square test and Student's *t*-test were used for the statistical analyses. A p value of less than 0.05 was considered to be significant.

Results

There were 15 case reports describing patients with visual disturbances due to AKA. There was no original report of treating such cases. Three reports were duplications; Thus a 12 case reports, including 4 English and 8 Japanese articles, were analyzed [7-18].

There were 14 patients who showed visual disturbances due to AKA. The background of these patients is shown in Tables 1 and Table 2. There were 11 males and 3 females. The range of age was from 44 to 68, with an average of 55 years old. Seven cases had loss of consciousness and the systolic blood pressure of 12 cases was under 90 mmHg. An arterial blood gas analysis showed that all cases had a pH under 6.90 and severe metabolic acidosis. All but one of the visual disturbance cases improved after correction of acidemia by infusion of sodium bicarbonate or blood purification. One case with blurred vision was not re-evaluated because of their immediate death following admission. The degree of visual disturbance was 11 cases of blindness, 2 cases of light perception only and one case of blurred vision. Six patients experienced cardiac arrest duration hospitalization. Four cases underwent cardiac arrest within several hours of arrival, one case within a day and one case within 2 days. Eleven cases required intensive care for organ failure and three patients died.

The results of comparison between the arrest and no-arrest group are shown in Table 3. There was no significant difference associated with the sex, age, frequency of consciousness disturbance and systolic blood pressure on arrival between the two groups. The average pH on arrival in the arrest group was smaller than that in the no-arrest group. Patients with severe AKA associated with pH under 6.70 tended to experience cardiac arrest (p=0.05). In addition, the survival ratio in the arrest group was smaller than that in the no-arrest group (50 vs. 100%).

Discussion

This manuscript successfully demonstrated that severe AKA was associated with the occurrence of visual disturbances that could be cured by correction of acidosis. In addition, patients with severe AKA with a pH under 6.70 tended to experience cardiac arrest. Patients with severe AKA that experience cardiac arrest have a poor prognosis.

Three previous reports demonstrated severe metabolic acidosis other than AKA is associated with reversible blindness [19-21]. Two of those cases were due to metformin-associated lactic acidosis and one case was diabetic ketoacidosis. The pH in the all three of the cases was under 6.90 (6.65, 6.64, 6.89) and their visual acuity recovered immediately after correction of metabolic acidosis, as observed in the current study. Ten of the current cases were in shock, suggesting that circulatory insufficiency may contribute to the occurrence of visual disturbances, because cardiac arrest, which is worst type of circulatory insufficiency, results in mydriasis with loss of light reflexes. However, there were no reports of isolated circulatory insufficiency without unconsciousness leading visual disturbances, suggesting that circulatory insufficiency was not the main cause of the visual disturbance. In addition, a high value of serum alcohol over 500 mg/dl could lead to mydriasis with loss of light reflexes due to inhibition of the central nervous system [22]. However, none of the patients in which the of serum alcohol concentration was measured showed such a high level of serum alcohol. Moreover, patients with severe AKA cannot drink alcohol, so the high concentration of serum alcohol itself was not the main cause of the visual disturbances. Furthermore, thiamine deficiency may contribute to the occurrence of visual disturbances. However, 9 of the patients in the current series denied the possibility of a thiamine deficiency. Some cases in this study demonstrated increased lactate levels when it was measured, but AKA commonly was associated with lactic acidosis, especially in patients with sepsis, seizures, thiamine deficiency, or impaired liver function [23,24]. AKA with lactic acidosis often was treated as AKA [23,24]. Accordingly, the main cause of visual disturbance was thought to be AKA or AKA with lactic acidosis.

Animal studies suggest that retinal cell function may be extracellular pH dependent. Fish and tiger salamander retinal horizontal cell's response to light is extracellular pH sensitive, and mammalian retinal cell function becomes disrupted at a extracellular pH of less than 7.0 [25-27]. In addition, the activation of acid-sensing ion channels by protons, which are the proton-gated cation channels widely expressed in peripheral sensory neurons and in the neurons of the central nervous system, has been reported to play an important role in a variety of physiological and pathological processes such as nociception, mechanosensation, synaptic plasticity, and acidosis-mediated neuronal injury [28]. These effects may extend to humans and may serve as an

No.	Age	Sex	Alcohol intake	Alcohol history	Conscious Level	Pupil diameter	Light reflex	Systolic BP
unit	Year		g/day	year		mm		mmHg
1	66	Male	?	24	Alert	4	none	82
2	53	Male	100	20	Semicoma	6	none	90
3	63	Male	?	?	Alert	?	?	90
4	44	Male	200	over 5	Alert	7	none	80
5	59	Male	170	40	Alert	4	sluggish	73
6	48	Male	180	over 8	Semicoma	7	none	87
7	61	Male	?	?	Disoriented	5	?	65
8	49	Male	?	?	Alert	?	?	73
9	48	Female	over 110	?	Disoriented	?	sluggish	134
10	68	Male	?	?	Disoriented	3.5	none	150
11	56	Male	?	?	Disoriented	5	none	79
12	49	Female	?	?	Alert	3	none	130
13	43	Male	180	over 10	Disoriented	?	?	80
14	57	Female	?	?	Alert	Dilated	sluggish	120

Table 1: Background of subjects_regarding age, sex, and physiological findings.

No.	pH	PCO_2	PO_2	HCO_3	Base Excess	Lactate	Glucose	Alcohol	BHBA	AAA	Thiamine_ deficiency_IC	Require of DH	Arrest	Outcome
unit	mmHg	mmHg	mmHg	mg/dl	mg/dl	mmol/l	mmol/l	mg/dl	μmol/l	μmol/l				
1	6.855	13.9	190.5	2.5	-31.4	?	69	45.8	140	14	no	yes	no	survival
2	6.497	51	?	3.8	-29	?	?	8	1190	332	No	yes	yes	survival
3	6.612	14	?	1.5	-28	?	?	not exam	6360	261	no	yes	yes	survival
4	6.707	13.6	272.8	1.6	-30	?	91	0	245	11	no	yes	yes	death
5	6.748	13	134	1.7	-33	270	70	not exam	2160	220	no	yes	no	survival
6	6.748	20.3	151	2.6	-33.9	297	85	27.4	?	?	not exam	Yes	no	survival
7	6.623	35.0	231	3.5	-34	?	?	?	2960	460	no	yes	yes	death
8	6.78	15.5	118	2.3	-31	?	?	?	?	?	no	no	no	survival
9	6.64	8.3	159	?	-37.5	109	153	not exam	823	272	no	yes	yes	survival
10	6.79	11.8	137.2	1.8	-33	?	38	not exam	4825	210	not exam	yes	no	survival
11	6.55	44.4	198	3.7	-29.4	?	20	not exam	not exam	not exam	not exam	yes	no	survival
12	6.79	8	196	?	?	90	?	68	?	8.82	no	?	no	survival
13	6.74	22.4	88	2.7	-36	?	255	not exam	not exam	not exam	not exam	yes	yes	death
14	?	?	?	<3.3	?	625	150	?	?	?	?	no	no	survival

BHBA: β-hydroxybutyrate acid, AAA: acetoacetate acid, BP: blood pressure, IC: intensive care, DH: during hospitalization, ?: not described, exam: examination

Table 2: Background of subjects regarding the laboratory data and outcome.

	Arrest	No-Arrest	p-value
	n=6	n=8	
Age	52.0 + 3.4	56.5 + 2.7	n.s.
Sex (Male/Female)	5/1	6/2	n.s.
Consciousness (number of alert)	2	5	n.s.
Systolic blood pressure (mmHg)	89.8 + 9.5	99.2 + 10.5	n.s.
pH	6.637 + 0.035	6.752 + 0.036	0.04
PCO_2 (mmHg)	24.0 + 6.6	18.1 + 4.6	n.s.
HCO_3^- (mmol/l)	2.6 + 0.4	2.4 + 0.2	n.s.
Survival	3	8	0.02

n.s.: not significant

Table 3: Results of an analysis between Arrest and No-Arrest groups.

explanation for acidosis-associated vision loss. An AKA patient with pH 6.497 and hypotension did not demonstrate visual disturbance until his death [3]. Accordingly, both the severity and duration of acidosis might contribute to induce visual disturbances due to AKA.

More severe acidosis with visual disturbance due to AKA tended to have cardiac arrest. An animal study demonstrated that severe acidosis causes a decrease in ventricular performance by a direct depressant effect on the myocardium, impairs the myocardial response to catecholamine, decreasing cardiac muscle contractility and causing endocardial damage [29-32]. In addition, the energy crisis induced by impairment of fat and glucose metabolism or direct injury to the mitochondria due to excessive ethanol intake might directly suppress cardiac output [33]. However, no previous studies have so far proven this hypothesis. The low cardiac output induced by severe acidosis is also exacerbated by hypovolemia, hypoxia, and hypothermia, with each different factor also leading to low cardiac output, and severe AKA tended to be associated these complications [3,34]. Accordingly, physicians should understand the importance of timely and appropriately treating severe AKA patients with visual disturbances.

Conclusion

Severe AKA of itself resulted in the occurrence of visual disturbance, which could be cured by correction of acidosis. In addition, patients with severe AKA with an arterial gas pH under 6.70 tended to experience cardiac arrest. Accordingly, physicians should understand how to treat such patients.

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