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Case Report

Oral Supportive Nutrition Induces Hypocupremia, Hypercholesterolemia and Potassium Increasing

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ABSTRACT

In Japan, two million of in patients require intensive care, and a large proportion of these patients are bedridden. One of the problems encountered in the care of bedridden patients is their poor nutritional condition. To treat such a condition, tube feeding combined with intravenous drip administration is frequently used in hospitals. However, despite adequate nutritional support, bedridden patients in tube feeding tend to be malnourished. We have recently reported on the case of an elderly female patient with hypocupremia who was fed with only supportive nutrition that contained very low levels of copper (Cu) showed hypoleukemia and hypercholesterolemia. However, it has not clarified whether these changes are induced by the supportive nutrition administered and/or hypocupremia itself. To clarify the issue, in the present study, we collected data on the condition of meal intake and several laboratory data from the medical records of inpatients. As a result, we concluded that low-Cu supportive nutrition (LCuSN) induces hypocupremia and hypercholesterolemia. LCuSN also induces decrease in albumin and increase in concertation of potassium, potentially induces hypoalbuminemia and hyperkalemia. However, LCuSN does not induce hypoleukemia.

1. INTRODUCTION

In the case of inpatients in psychiatric hospitals in Japan, long-term hospitalization is a problem that has been noted for a long time now by not only Japanese medical doctors but also specialists from other countries.[1] Some critical approaches have been proposed and implemented to shorten the duration of hospitalization.[2-4] However, there are still many patients who are hospitalized for more than five years in Japanese psychiatric hospitals.

Another problem of long-term hospitalization is aging-related disorders such as frailty, cardiovascular disorders, metabolic disorders, and cancer. Most of these disorders become do not always lead to sudden death of the patients. Most of these patients, unfortunately, become disabled or bedridden. In

Japan, although there is no current epidemiological survey of the number of bedridden patients, two million of patients require intensive care (over long-term care level 3, categories 3 and above of 7 categories of social care; Annual reports on the aging society from cabinet office, government of Japan, 2017 fiscal year edition) and a large proportion of these patients are bedridden.

One of the problems encountered in the care of bedridden patients is their poor nutritional condition.[5,6] They lose their appetite and ability to swallow, which reduce the total amount of their nutrition of intake. To improve their condition, tube feeding combined with intravenous drip administration is frequently used in hospitals. However, despite adequate nutritional support, bedridden patients on tube feeding tend to be malnourished.[5,6]

We have recently reported on the case of an elderly female patient with hypocupremia was fed with only supportive nutrition that contained very low levels of copper (Cu).[7] She showed a decrease in the count of white blood cells (WBCs) and an increase in the level of total cholesterol (T-chol). However, it has not been whether these changes are induced by the supportive nutrition administered and/or hypocupremia itself. To clarified this issue, in the present study, we collected and analyzed data on the condition of meal intake and several laboratory data.

2. CASE PRESENTATION

We summarized the laboratory data collected from medical record of patients 65 years old and older admitted to Johmoh Hospital from January, 2015 to August, 2018, and whose serum Cu levels were measured. Some of them were included in the analysis more than twice at different time points. The main diagnoses of these patients are shown in Supplemental Table 1. The patients were then categorized into two groups depending on the type of nutritional support provided at least one month before blood sampling; low-Cu supportive nutrition (LCuSN) and general nutrition (GN). Patient in LCuSN group intake LCuSN because of decrease in appetite by several mental disease such as dementia, swallowing problem including tooth trouble, and gastrointestinal diseases. All data were compared by one-way ANOVA. Post-hoc comparison was performed by Student's t-test using Excel Statistics (Esumi). Logistic regression analysis was performed using EZR.[8] Differences were considered significant at p <0.05. All values are presented as mean±SEM.

As shown in Supplemental Table 1, the number of male patients was small in this study. The percentage of bedridden patients was high among males. In Table 1, the male GN group was significantly younger than the male LCuSN group. Note that these differences did not affect the main results of this study.

Table 2 clearly shows that LCuSN induced hypocupremia, and as we reported, hypercholesterolemia.[7] The odds ratio of these changes was significantly high. However, the counts of RBCs and WBCs, and the level of Hb did not significantly change and were normal. We found that concentration of Alb was lower than the normal range; and was statistically significantly different from that in the GN group. Also the concentration

Table 1. Background features of each group.

	LCuSN	GN
Age		
All	80.7±2.0	79.1±0.5
Male	78.8±4.4	73.0±0.8*
Female	82.0±1.9	81.4±0.6
N [data (patients)]		
Male [101 (20)]	6 (3)	61 (18)
Female [263 (32)]	9 (7)	158 (32)

*indicats statistically significant difference at p=0.0385 by Student's t-test.

Table 2. Laboratory data.

		LCuSN	GN	p	OR	95%CI	p
Cu (μg/dL)		62.8±10.5	103.4±1.4	<0.0001			<0.000
RBCs (10^4 cell/μL)	Male	394.7±35.6	397.4±7.6	0.919			
	Female	386.9±17.4	387.1±4.5	0.991			
WBCs (cell/μL)		5,949.3±471.9	5,772.2±99.2	0.657			
Hb (g/dL)	Male	12.2±1.1	12.2±0.2	0.906			
	Female	11.9±0.5	11.8±0.1	0.751			
Plt (10^4 /μL)		26.1±2.6	23.7±0.4	0.205			
TP (g/dL)		6.8±0.12	6.7±0.04	0.549			
Alb (g/dL)		3.0±0.08	3.2±0.03	0.0381	3.01	0.825-11.0	0.0951
Na (mEq/L)		136.1±1.2	138.7±0.2	0.0542			
K (mEq/L)		4.4±0.11	4.1±0.03	0.0173	2.31	0.785-6.82	0.128
Cl (mEq/L)		99.3±0.9	101.1±0.2	0.0560			
T-chol (mg/dL)		200.5±15.3	164.3±2.6	0.0009	5.94	1.82-19.4	0.00313

Table 3. Modified odds ratio.

	OR	95%CI	*p*
Cu	25.3	6.85-93.5	<0.0001
Tchol	15.6	3.52-69.3	0.0003

Odds ratio modified by age, gender, BMI, and activity-level.

of potassium was significantly higher in the LCuSN group than in the GN group. However, the odds ratio of these changes was not statistically significant.

As mentioned above, the gender, age, and activity level of each group were not normalized in this study. BMI also potentially correlated with hypocupremia and hypercholesterolemia regardless of the type of supportive nutrition. As shown in Table 3, however, the modified odds ratios for hypocupremia and hypercholesterolemia remained statistically significantly different.

We concluded that the type of supportive nutrition given to elder patients induced hypocupremia and hypercholesterolemia. The type of supportive nutrition also induces decrease in concentration of albumin and increase in concentration of potassium, which potentially induced hypoalbuminemia and hyperkalemia. However, hypocupremia did not induce anemia or leukopenia.

3. DISCUSSION

Cu is one of the essential trace elements because it acts as a critical cofactor of specific cuproenzymes that catalyze electron transfer reactions required for cellular respiration, iron oxidation, pigment formation, biosynthesis of neurotransmitters, antioxidants, and defensins, peptide amylation, and connective tissue formation.[9] However, Cu deficiency in humans has been considered a rare condition because Cu is widely distributed in food sources. Acquired Cu deficiency has been observed in hospitalized patients treated with long-term total parenteral or enteral nutrition lacking copper supplementation.[10-13]

3.1. Cu and Food Intake; Hypocupremia Induced by Supplemental Oral Liquid Diet

Cu is included in several foods, and hypocupremia is very rare. However, poor nutrition conditions, such as total parenteral or enteral nutrition, potentially induces hypocupremia. As shown in the present study, very unique conditions (Cu-free food intake for several months) potential induce hypocupremia.

Klevay et al. reported that low-Cu nutrition induces the increase in cholesterol levels.[14] They also reported that Cu replenishment returned the concentration of cholesterol to normal levels. However, the concentrations of Cu and lipids condition are still controversial.[15-17] In this study, LCuSN includes high fat levels to increase the calorie. This somehow, contributes in maintaining blood parameters (numbers of blood cells, Hb levels, and TP/Alb) within normal ranges. However, as shown in this study, high fat levels potentially induced hypercholesterolemia, which is the typical risk factor for cardiovascular diseases.

Anemia is one of the common disorders induced by hypocupremia.[11,12,18,19] In this study, however, hypocupremia induced by LCuSN did not induce anemia. There is a possibility that homeostasis of (super-)elderly patients in this study masked the effect of hypocupremia on anemia. Further study should be carried out to clarify the relationship between hypocupremia and anemia in elderly patients.

Elderly people, especially those with dementia, frequently lose their appetite and have decreased the food intake. However, sometimes they can be encouraged to eat again via psychological factor (e.g., use of different type of nutrition, considering food preferences), which will usually be easier to implement than drug medication.

3.2. Cu and Iron Levels; Hypocupremia Potentially Induces Hyperkalemia

As far as we know, there is no report about hypocupremia inducing hyperkalemia. Because Cu participate in several metabolic cascades in the human body, multiple pathways are involved in the increase in the concentration of K in serum. Srivastava et al. reported that a low Cu concentration potentially decreases the extracellular concentration of K.20 In potassium channel, KCa3.1, Cu plays a role in the inactivation of channels.20 Thus, if the concentration of Cu decreases, the activity of KCa3.1 is potentially enhanced and concentration of K in serum will be increased. Further study is necessary to clarify the mechanisms underlying these phenomena.

At least from the results of our study, the concentration of Cu in serum potentially changes the concentration of K in serum. Since hyperkalemia potentially induces lethal arrhythmia, considering the concentration of Cu as a risk factor for hyperkalemia could be a new future perspective in medication.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Supplemental Table 1. Background features of patients.

	Male	Female
Number of patients	20	32
Average hospitalization duration	1,582.2±711.4 days	1,589.2±325.3 days
Percentage of patients who were unable to walk by themselves	85.0% (17)	84.4% (27)
Percentage of bedridden patients	60.0% (12)	28.1% (9)
Main diagnosis		
Schizophrenia	7	11
Alzheimer syndrome	4	5
Geriatric psychosis	4	7
Depression	0	5
Cardiovascular disease	1	3
Hypertension	5	7
Diabetes mellitus	3	1

Some patients had their blood sample collected several times; thus, one patient may be categorized into several groups. We categorized patients who mainly had general nutrition (GN) twice per day for more than 20 days per month into the GN group. Patients who were mainly given low-Cu supportive nutrition (LCuSN) twice per day for one month were categorized into the LCuSN group, which was a critical criterion. We excluded data that were obtained under different feeding conditions. We also excluded data obtained when patients had infections determined on the basis of C-reactive protein levels. A patient whose blood was sampled several times under different feeding conditions was included in several groups. The data of the patient previously reported were also included.