Clinical Features of Hematological Disorders Caused by Copper Deficiency during Long-Term Enteral Nutrition

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Abstract

Objective Copper deficiency has been reported to cause hematological disorders. However, its clinical and hematological characteristics are not fully understood. Therefore, we investigated bedridden patients suffering from copper deficiency and tried to clarify the clinical features of hematological disorders caused by this condition.

Patients and Methods Five patients with typical copper deficiency who had been dependent upon enteral nutrition for a long period of time due to various diseases were investigated. We measured hematological parameters and observed the response to copper supplementation therapy and the recovery process of hematological disorders.

Results Their mean age was 82.6±10.4 years and the mean duration of enteral nutrition was 16.4±5.2 months. Their serum copper concentration was extremely decreased (range, 3 to 8 μg/dl). All five patients had anemia and neutropenia. On the other hand, platelet count remained within the normal range. After copper supplementation therapy, hemoglobin concentration increased from 6.8±0.7 g/dl to 9.9±0.7 g/dl within a few months (p<0.01). Neutrophil count also increased from 750±370/μl to 3,690±1,210/μl in a few weeks (p<0.01). Mean corpuscular volume (MCV) decreased from 94.3±7.3 fl to 86.0±4.8 fl (p<0.05). Elevated serum ferritin and erythropoietin (EPO) levels were normalized after the improvement of anemia.

Conclusion Bicytopenia (anemia and neutropenia) with normal platelet count is a feature of hematological disorders caused by copper deficiency. MCV tends to indicate macrocytic anemia. Serum ferritin and EPO levels are elevated. These hematological abnormalities are improved within a few months after copper supplementation therapy.

Key words: copper-deficient state, hematological disorders, anemia, neutropenia, enteral nutrition, copper supplementation therapy

Introduction

Copper is known as an essential trace element and is widely distributed in food sources. Copper deficiency in humans has been considered a rare condition. An inherited form of copper deficiency is Menkes’ kinky hair syndrome with degeneration of central nervous system and hair abnormalities; it is a disease due to a defect in the intestinal copper absorption (1). Acquired copper deficiency has been reported in premature or malnourished infants (2, 3) and in patients treated with long-term total parenteral or enteral nutrition lacking copper supplementation (4–12). Less commonly, intestinal malabsorption after partial gastrectomy is also associated with copper deficiency (13, 14). Moreover, copper deficiency can occur as a result of long-term ingestion of high amounts of zinc, because the metabolism of copper and zinc are linked (15–17). In infants, copper deficiency causes various complications such as hematological, skeletal, and neurological disorders, whereas hematological disorder is a major clinical manifestation in adults.

In recent years, associated with the increase of the elderly patients who are bedridden due to cerebrovascular diseases or dementia, copper-deficient patients who depend up on long-term total parenteral or enteral nutrition have increased. In 1972, Karpel and Peden (4) reported the first case of anemia and neutropenia in a patient receiving total parenteral nutrition. Since then, increasing reports of copper-deficient patients receiving total parenteral or enteral nutrition have been published (5–12). Although it is generally known that
Copper deficiency causes peripheral blood cytopenias, typically anemia and neutropenia, the details of its clinical and hematological characteristics are not fully understood. Recently, we encountered several typical patients who suffered from hematological disorders caused by copper deficiency during long-term enteral nutrition. The present study was conducted to clarify the clinical features of hematological disorders caused by this condition.

Patients and Methods

Patients

We measured the serum copper concentration in all eight patients admitted to Hasaki Saisei Hospital (presently Kamisu Saiseikai Hospital) in November 1998, who had been dependent upon enteral nutrition for a long period of time. Serum copper concentration (normal range: 78–131 µg/dl) was measured by atomic absorption spectroscopy (SRL Co., Ltd., Tokyo, Japan). In all patients, serum copper concentration was low, and especially in five of them, it was severely decreased (less than 10 µg/dl). We investigated the clinical and hematological features of the five patients, and observed the response to copper supplementation therapy and the recovery process of hematological disorders. The other patients whose serum copper concentration was mildly or moderately decreased were excluded from the study.

Methods

In the five patients, just before the start of copper supplementation therapy, complete blood cell count, reticulocyte count, serum iron, unsaturated iron binding capacity (UIBC), ferritin, erythropoietin (EPO), zinc, vitamin B₁₂, folic acid and other biochemical parameters were measured using standard laboratory methods.

After obtaining written informed consent from their families, a daily dose of 3 mg of copper using a 0.04% copper sulfate solution was administered via a nasogastric tube. The copper sulfate solution was administered soon after the administration of the enteral diet three times a day. From the start of copper supplementation therapy, hemoglobin concentration, mean corpuscular volume (MCV), reticulocyte count, neutrophil count, platelet count and other biochemical parameters were measured once a week for the first ten weeks and thereafter at adequate intervals. In addition, in some cases, the values of serum ferritin and EPO measured before and after copper supplementation therapy were compared.

Statistical analysis

The values were expressed as mean values±S.D. Statistical differences in mean values were analyzed using paired t-test. Differences were considered as statistically significant at p<0.05.

Results

Clinical background

The clinical characteristics of the patients are shown in Table 1. There was one male and four females. Their mean age was 82.6±10.4 years and serum copper concentration ranged from 3 to 8 µg/dl (normal range: 78–131 µg/dl). All the patients had consciousness disturbance (Japan Coma Scale 100–300) and were bedridden because of cerebral infarction (2 cases), cerebral hemorrhage (1 case), subarachnoidal hemorrhage (1 case) and senile dementia (1 case). Their nutrition had depended completely upon enteral nutrition for more than 12 months (16.4±5.2 months). All the patients were given 600–900 ml (1.5 kcal/ml) of enteral diet (Isocal Plus, Bristol-Myers Squibb Co., Ltd., Tokyo, Japan) each day. This diet contained 0.005 mg copper/100 kcal, which was insufficient for adult copper requirement.

Hematological and laboratory findings at the start of copper supplementation therapy

Laboratory data at the start of copper supplementation therapy are shown in Table 2. All the patients had moderate to severe anemia. Mean hemoglobin concentration was 6.8±0.7 g/dl (range, 6.0 to 7.8 g/dl) and MCV tended to indicate normocytic or slightly macrocytic anemia (range, 83 to 100 fl). Reticulocyte count was within the normal range. In all patients, neutropenia was observed. On the other hand, all patients had a normal platelet count. The serum iron level was decreased and the UIBC was within normal limits in all patients. The serum ferritin level was elevated in three patients and the other two patients had a normal serum level. EPO was elevated in all patients, and the serum level of zinc was normal or slightly decreased. Vitamin B₁₂ did not show

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Underlying disease</th>
<th>Duration of enteral nutrition (months)</th>
<th>Serum copper concentration (µg/dl)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>95</td>
<td>F</td>
<td>Cerebral infarction</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>67</td>
<td>F</td>
<td>Senile dementia</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>81</td>
<td>F</td>
<td>SAH</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>M</td>
<td>Cerebral hemorrhage</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>F</td>
<td>Cerebral infarction</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

constant tendency. Folic acid level was normal or slightly elevated. The serum C-reactive protein (CRP) level was almost within the normal range, except for one patient (Patient 3). Patient 3 was suffering from urinary tract infection at that time, however, her CRP level became negative promptly after antibiotic therapy. Parameters of liver function (aminotransferase) were within normal limits in all patients but mild elevation of serum creatinine was observed in two patients (Patient 4; 1.9 mg/dl and Patient 5; 1.7 mg/dl, respectively). Patient 2 died of pneumonia at nine weeks and Patient 5 died of multiple organ failure at four weeks after the start of copper supplementation therapy.

Effect of copper supplementation therapy on hematological parameters

Figure 1 shows changes in hemoglobin concentration and reticulocyte count associated with copper supplementation therapy. Hemoglobin concentration gradually increased from 6.8±0.7 g/dl to 9.9±0.7 g/dl within a few months (p<0.01). The average hemoglobin concentration after copper supplementation was calculated based on the values at ten weeks (In Patient 2 and Patient 5, the values at nine weeks and at four weeks were used, respectively). Transient brisk reticulocytosis was observed especially in Patient 1 and Patient 3. Neutrophil count also rapidly increased from 750±370/μl to 3,690±1,210/μl in three weeks (p<0.01), as shown in Fig. 2. MCV significantly decreased from 94.3±7.3 fl to 86.0±4.8 fl (p<0.05), as shown in Fig. 3. The average MCV after copper supplementation was calculated in the same way as that of hemoglobin concentration.
Adverse events induced by copper supplementation therapy

None of the patients developed adverse events related to the administration of the copper sulfate solution at the doses employed in this study.

Case presentation

Figure 4 shows the clinical course of a patient who showed a remarkable response to copper supplementation therapy. The patient, a 95-year-old woman (Patient 1), was bedridden due to cerebral infarction and had been dependent entirely upon a low copper enteral diet for 23 months. She had severe anemia. Initially the etiology of her anemia was unknown and blood transfusion was needed. However, the measurement of serum copper concentration revealed that she was in a severe copper-deficient state. Her serum copper concentration was 7 µg/dl. Her hemoglobin concentration gradually increased from 6.0 g/dl to 9.8 g/dl after ten weeks of copper supplementation therapy at a daily dose of 3 mg and reached the normal level (13.3 g/dl) one year later. The neutrophil count also increased from 418/µl to 2,719/µl in two weeks and remained at values within the normal range thereafter. Both serum ferritin and EPO levels, which showed high values before copper supplementation therapy, decreased to the normal range one year later. At that time, her serum copper concentration had increased to 106 µg/dl.

Discussion

Iron deficiency anemia is a common nutrient deficiency-induced hematological disorder. In contrast, copper deficiency has been reported in rare cases, such as Menkes’ syndrome which is a hereditary disease (1), premature infants and malabsorption syndrome in infancy (2, 3). However, associated with the increase of bedridden elderly patients in recent years, a special situation has presented, that is, numerous patients have become dependent upon long-term total parenteral or enteral nutrition. Consequently, the patients suffering from hematological disorders caused by acquired copper deficiency have also increased (4–12).

In Japan, many commercially available enteral diets contained very low amount of copper, since the addition of trace elements was prohibited by the Food Sanitation Law. Therefore, it is considered that long-term enteral nutrition using these diets easily leads to a copper-deficient state. The five patients investigated in the present study were nourished solely by copper-deficient enteral diets for a prolonged period (16.4±5.2 months). The amount of copper administered to our cases was estimated to be 0.045 to 0.067 mg a day, which was approximately one-tenth of the recommended daily requirement (18). As a result, their serum copper concentrations showed remarkable low values.

In addition to extremely low levels of copper, the restoration of the patient’s anemia and neutropenia after oral administration of a copper sulfate solution confirmed that copper deficiency was the cause of these hematological abnormalities. We found the following common features in this study: 1) Hematological disorders caused by copper deficiency were characterized by anemia and neutropenia. On the other hand, the platelet count remained within the normal range. 2) MCV tended to indicate macrocytic anemia and decreased after copper supplementation therapy. 3) Serum ferritin and EPO levels were elevated and decreased to values within the normal range after the improvement of anemia. 4) The improvement of anemia took a few months and neutropenia improved in a few weeks after the start of copper supplementation therapy.
Although there are a few reports showing that copper deficiency causes pancytopenia (12, 19–21), the majority of investigators report that bicytopenia (anemia and neutropenia) is a common manifestation of copper deficiency, the same as observed in this study. Neutropenia is considered indispensable to establish the diagnosis of copper deficiency-induced hematological disorders. In fact, although we also administered a copper sulfate solution to the patients with mild to moderate copper deficiency who had anemia, but not neutropenia, their anemia did not improve (data not shown), showing that copper deficiency was not the cause of anemia in these patients. On the other hand, all of our patients had a normal platelet count. It is considered that the development of thrombocytopenia is rare. However, a more prolonged copper-deficient state might be necessary for the development of thrombocytopenia. We cannot completely exclude the possibility that our patients were at risk of developing thrombocytopenia.

As seen in Patient 1 (case presentation), elevated serum ferritin and EPO levels were normalized and MCV showed a decrease after copper supplementation therapy. This case is considered a typical example of a patient suffering from severe copper deficiency. The anemia of copper deficiency has been variously described as microcytic, normocytic, or macrocytic, and there have been few previous reports referring to changes of these parameters. In the present study, our patients had almost similar hematological features and showed similar responses associated with copper supplementation therapy. Therefore, these findings (elevated ferritin and EPO levels and macrocytic anemia) are considered to express genuine characteristics of copper deficiency.

The exact mechanism of copper deficiency-induced anemia and neutropenia has not been fully elucidated as yet. In the literature, several mechanisms have been supposed. It is speculated that failure to transform Fe$^{2+}$ into Fe$^{3+}$ due to a decreased level of ceruloplasmin leads to disturbance of iron transportation and thereby to an iron deficient state (22). Another speculated mechanism is that a decreased activity of superoxide dismutase, which is one of the copper-containing enzymes, hampers the removal of superoxide and leads to the injury of the cell membranes resulting in a shorter erythrocyte life span (8). Moreover, there are reports that in a copper-deficient state, the maturation of granulocytic stem cells is suppressed \textit{in vitro} (23) and heme production by heme synthetase is disturbed (24). On the other hand, there is a report suggesting that anti-neutrophil antibody is responsible for copper deficiency neutropenia (25). In this report, the neutrophil count was normalized and anti-neutrophil antibody production became negative or decreased after copper supplementation therapy. In the present study, their anemia was accompanied with a low reticulocyte count and a transient brisk reticulocytosis was observed in response to copper supplementation. Furthermore, although not examined in our patients, the bone marrow morphologic findings suggest an immaturity of erythroid and myeloid cells (26). These observations collectively suggest that copper-containing enzymes would play an important role in both cell differentiation and proliferation in the bone marrow, and that these hematological disorders are mainly due to an impairment in both erythroid and myeloid maturation and, in part, to reduced erythrocyte and neutrophil life spans.

Recently, the importance of trace elements has been
widespread in patients who depend upon long-term enteral nutrition. As a result, enteral diets, which are rich in trace elements such as copper, zinc and selenium, have been developed. It is expected that using these enteral diets will decrease the patients suffering from nutritional trace element deficiency in the future. However, copper deficiency-induced hematological disorders are still prone to be overlooked in daily clinical practice. Gregg et al (14) reported an interesting case of a copper-deficient patient. The patient was initially diagnosed as myelodysplastic syndrome and bone marrow transplantation was scheduled. However, just before the bone marrow transplantation, she was found to be in a severe copper-deficient state and recovered with copper supplementation. Her copper deficiency was due to malabsorption after partial gastrectomy. Once diagnosed, the copper-deficient state is easy to correct and hematological abnormalities can be quickly resolved with copper supplementation. Therefore, it might be advisable to measure the serum copper concentration in patients that have unexplainable cytopenias, especially anemia and neutropenia.

References