CASE REPORT

A Patient with Severe Iron-Deficiency Anemia and Memory Disturbance

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A 56-year-old woman presented with severe iron-deficiency anemia and memory disturbance. She had been in a state of severe iron deficiency for many years due to an unbalanced diet. Aerobic exercise test revealed an abnormal elevation of lactate and pyruvate reflecting mitochondrial dysfunction. After iron replacement therapy, WAIS verbal IQ score improved from 63 to 83, and levels of lactate and pyruvate on aerobic exercise test were normalized. We raise the possibility that severe and long-term iron deficiency anemia may cause memory disturbance due to mitochondrial dysfunction. (Internal Medicine 31: 1306-1309, 1992)

Key words: mitochondrial dysfunction, aerobic exercise test

Introduction

Iron is a heavy metal of biological importance not only as a component of hemoglobin but also as a constituent of enzymes of the electron transport system within mitochondria, in the form of heme in the cytochromes, and in the form of non-heme iron (1-3). It has become apparent that iron deficiency causes various systemic diseases with decreased concentration of mitochondrial cytochromes in tissues, as well as iron-deficiency anemia (IDA) (1-6). Recently it was reported that inhibition of cytochrome oxidase causes impairment of learning and hippocampal plasticity (7).

We report a case of severe iron deficiency anemia in a patient who suffered from memory disturbance. She had been in the state of severe iron deficiency for many years due to an unbalanced diet. Aerobic exercise test revealed an abnormal elevation of lactate and pyruvate characteristic of mitochondrial dysfunction. The findings in the present case suggest that severe iron deficiency may cause memory disturbance due to hippocampal dysfunction arising from mitochondrial disorder.

Case Report

A 56-year-old right-handed woman with approximately a 40-year history of unbalanced diet was admitted to our hospital for memory disturbance. She did not take any regular meals or drink milk, because of avoidance. After the management of completion of junior high school, she helped her sister’s grocery store. At 54 years of age, she was noted to make mistakes in the making of change and sometimes she could not remember whether she had received the money from the customer or not. These memory disturbances worsened slowly, and at 56 years of age, she was no longer able to work at the store. Her family noted personality change, she became stubborn and unconcerned with her appearance. She had not complained of general fatigue, dizziness or palpitation for the past 40 years. She was admitted to our hospital on September 14, 1990, because her memory disturbance had progressed.

General physical examination revealed that her height was 153cm and weight 47.6kg. Her blood pressure was 114/70mmHg and pulse 72 per minute. Her skin was pale, and palpebral conjunctiva was markedly anemic. Furthermore, she had severe spoon nail. There was grade-2 systolic murmur at the apex, but there was no lymphadenopathy or hepatosplenomegaly.

Neurological examination revealed that she was alert and cooperative. She had no cranial nerve palsy, pyramidal, extrapyramidal signs, cerebellar ataxia or muscle weakness. Neuropsychological status was evaluated using the Wechsler Adult Intelligence Score (WAIS),
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Mini Mental State Examination (MMSE), Miyake's Memory Test (MMT), Raven's Coloured Progressive Matrices (RCPM) and other tests. These examinations revealed low intelligence; WAIS verbal IQ score was 63 (Fig. 1), and MMSE score was 15. She showed particularly severe impairment in memory function, but she had only slight disorientation as to time and place, and no other focal signs such as right-left disorientation, finger agnosia, color agnosia, visuo-spatial agnosia, or con-

Fig. 1. WAIS verbal IQ scores before and after iron replacement. Her WAIS verbal IQ score increased from 63 to 83 after iron replacement. closed circles: before iron replacement. open circles: 80 days after iron replacement.

Fig. 2. Computed tomography of the brain showing cortical atrophy of the parieto-occipital lobes and mild dilatation of the temporal horn of the lateral ventricles suggesting atrophy of the hippocampus.
Hematological study revealed hypochromic microcytic anemia with a hemoglobin value of 4.3 g/dl, hematocrit of 19%, and red blood cell count of $3.31 \times 10^6$/ml. The white blood cell count was 2,900/ml with a normal differential count. Serum iron concentration was 6 μg/dl, and ferritin was 1 ng/ml. Examination of bone marrow smears revealed granulocyte/erythrocyte ratio of 1.0; there was erythroid hyperplasia, but no blastic cells were observed. Blood chemistry findings were all within normal limits. Serum vitamin (Vit.) concentrations were as follows: Vit. B1, 4.7 μg/dl (normal range: 1.5–6.0 μg/dl); Vit. B6, 2.5 ng/ml (4.5–20.0 ng/ml); Vit. B12, 290 pg/ml (230–830 pg/ml); and folic acid, 3.2 ng/ml (2.3–6.5 ng/ml).

Investigation of the etiology of IDA revealed no focus of chronic bleeding in the gastrointestinal tract or genitourinary tract. Intestinal malabsorption was ruled out, since the hemoglobin value was normalized after iron replacement therapy was begun (ferrous citrate sodium: 100 mg/day orally). Therefore, the IDA was apparently caused by the iron-deficient diet.

Computed tomography of the brain revealed marked cortical atrophy of the parieto-occipital lobe, and mild dilatation of the temporal horn of the lateral ventricle suggesting atrophy of the hippocampus (Fig. 2). Electroencephalographic findings were almost normal except for the few slow waves (6–7 Hz) at bilateral parietal lobes.

To evaluate the mitochondrial function, we measured serum lactate and pyruvate levels before and after exercise on a bicycle ergometer (15 watts, 15 minutes) (8). Her serum lactate and pyruvate levels were abnormally elevated after exercise, as occurs in mitochondrial encephalomyopathy (Fig. 3).

After 80 days of oral iron therapy, the hemoglobin concentration was normalized to 14.3 mg/dl and the red blood cell count increased to $5.26 \times 10^6$/ml. Furthermore, the levels of lactate and pyruvate during aerobic exercise test normalized (Fig. 3). At the same time, her WAIS verbal IQ score increased to 83, but the MMSE score remained unchanged.

**Discussion**

Although the present patient was diagnosed as having IDA and memory disturbance, the possibility of Alzheimer’s disease was not completely ruled out. Her neurological deficit was mainly memory disturbance without other cognitive dysfunction. Furthermore, her neuropsychological disturbance was improved by replacement of iron. Therefore, her memory disturbance was thought to be caused by iron deficiency rather than by Alzheimer’s disease.

Recently Bennett et al reported that the inhibition of cytochrome oxidase causes impairment of learning and
hippocampal plasticity in azide-treated rats (7). In the present case, the aerobic exercise test revealed abnormal elevations of lactate and pyruvate levels which were normalized by iron replacement therapy, suggesting that the patient had mitochondrial dysfunction (8, 9). From this evidence, one could speculate that the patient’s memory disturbance was caused by dysfunction of mitochondria in the hippocampus.

It has become evident in recent years that iron deficiency causes impairment in psychomotor development of infants and children (10). Memory disturbance is not generally encountered in patients with IDA. However, in the present case, the degree of iron deficiency was severe and the duration of anemia was thought to be longer than 40 years. The findings in the present case indicate that severe and long-term IDA may cause memory disturbance due to mitochondrial dysfunction.

References