A CLINICAL STUDY ON THIAMINE DEFICIENCY

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THAT thiamine deficiency induces myocardial changes is a well known fact, and beriberi heart disease is considered to be a representative disorder in the group of nutritional myocardial disease. In Japan, this disease was widespread in the past, and many patients died from it, the peak mortality reaching 26,797 in 1923. Then, as the knowledge of its etiology, thiamine deficiency, spread, beriberi heart disease diminished gradually and nearly disappeared, so that, in this country it was regarded to be a historical illness—until quite recently.

In the last four years, however, beriberi heart disease has reappeared, chiefly in the west part of Japan, centering on the younger generation, and we have experienced 23 cases in this time. Moreover, we observed thiamine deficiency in the patients with congestive heart failure which we treated with diuretics.

Thus, thiamine deficiency is not a matter of the past, but may have important implications even in modern cardiology. In the present study, the clinical features of our 23 cases are analyzed, and the effects of diuretics upon thiamine metabolism are examined in the patients with congestive heart failure.

I. Clinical Features of Beriberi Heart Disease

Age and Sex. The ages of the 23 patients were between 15 and 52 years; 17 patients were under 20 years and the remaining 6 were over 20 years. Nineteen males and 4 females. Thirteen patients were high-school boys.

Seasonal Incidence and Predisposing Factor. Twenty patients fell sick from summer to autumn. Eight were in athletics, and one, a 17 year old high-school boy, became ill just after 20 days of physical work in August. History of alcoholism, unlike Occidental beriberi, was observed in only one patient, a 52 year old male, but nearly all patients showed the dietary imbalance of excessive intake of carbohydrate. In the present study, we believe that beriberi heart disease was induced in patients with latent thiamine deficiency triggered by physical exertion in hot summer weather.

Symptoms and Signs. All of the 23 cases complained of leg edema. Numbness with gait disturbance was observed in only one case, while knee jerk was diminished in 6 and abolished in 2; the manifestation of peripheral neuritis being not so frequent in the present study.

Chest X-ray. The heart was either normal in size or enlarged slightly. The presence of cardiac enlargement in beriberi heart disease can be ascertained retrospectively with the diminution of heart size after treatment, and the average value of cardiothoracic ratio was decreased significantly (p < 0.001) from 51.0 ± 4.7 (mean ± SD) to 43.4 ± 4.8% with the administration of thiamine. Nearly half of our cases showed apparently normal cardiac silhouette with cardiothoracic ratio less than 50%, but even in these cases, the heart size definitely diminished after treatment, as shown in Fig. 1.

Electrocardiogram. There was an increase in heart rate and prolongation of QT interval. With treatment, heart rate decreased from 72.5 ± 18.8 to 59.7 ± 10.8/min (p < 0.01) and QTc from 0.428 ± 0.027 to 0.407 ± 0.023 sec (p < 0.001). In 19 of the 23 cases, the electrocardiogram disclosed inverted, diphasic or depressed T waves. These abnormalities of T wave occurred mainly in the right precordial leads, but, in some cases, also appeared in the left precordial and limb
Fig. 1. Chest X-rays of a 17 year old high-school boy.

The cardiothoracic ratio showed 47% before treatment (A). It decreased to 37% 8 days after the beginning of therapy (B) and 35% after 15 days (C). After about 6 months (D), it still remained 34%, in spite of the discontinuation of the therapy. In this case, the cardiac silhouette appeared apparently normal at first, but it diminished perceptibly after treatment, revealing retrospectively the presence of cardiac enlargement at the time of illness.

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leads. These changes of T waves were not specific for beriberi heart disease, but could be improved with treatment as shown in a case of Fig. 2, revealing retrospectively the significance of T-abnormalities in this disease.

**Hemodynamics.** In 13 cases, hemodynamic studies were performed with the analog simulation method of radiocardiogram. The patients were divided into 2 groups based on their ages: 8 cases into a younger group of under 20 years and 5 into an elder group of over 20. The changes of parameters such as cardiac index, heart rate, stroke index, peripheral vascular resistance, turn-over rate of blood and circulating blood volume were all marked in the younger group, but mild in the elder one. In 5 cases of the younger group, who were studied at the early stage of the disease, there were prominent increases of cardiac index (7.93 ± 0.83 1/min/m²), stroke index (97.4 ± 7.5 ml/m²) and circulating blood volume (3.54 ± 0.21 l/m²), and a marked decrease of peripheral vascular resistance (454.6 ± 48.7 dynes·sec·cm⁻⁵). All these values showed significant differences compared to that obtained in the elder group (p < 0.001).

In the present cases, thiamine deficiencies in the younger and elder groups were approximately the same; that is 2.22 ± 1.18 and 2.40 ± 0.95 μg/dl in blood thiamine concentrations, 363 ± 141 and 359 ± 197 μg/ml/hr in erythrocyte transketolase activities and 54.8 ± 41.0 and 58.4 ± 40.4% in thiamine pyrophosphate effects, respectively.

Therefore, the characteristic features of beriberi heart disease were predominantly observed in young patients under 20 years old, while the elderly patients had the obscure symptoms even when suffering from the same degree of thiamine deficiency, reflecting the slight changes of hemodynamics. The exact mechanism of such differences between the young and elderly patients is still unknown. However, the varied need for thiamine with respect to age is considered to play a important role. In addition, the organic changes of the myocardium induced by the continued lack of thiamine may modify the original pathophysiology of beriberi heart disease in elderly patients. It is supposed that there might be numerous cases with latent thiamine deficiency among the elder generation without recognizable clinical manifestations.

**Diagnostic Criteria.** On the basis of the pres-
ent observations, diagnostic criteria is shown in Table I, with reference to that of Blankenhorn and Wagner. In young patients, beriberi heart disease is readily suspected from their clinical features, and the diagnosis is established with the dramatic amelioration after thiamine administration. In elderly patients, however, the clinical features are frequently atypical as mentioned above. Sometimes, the sufficient supply of thiamine fails in treating the clinical features in cases with an unquestionable thiamine deficiency. In such cases, we cannot readily distinguish beriberi heart disease showing irreversible changes at the advanced stage, from latent thiamine deficiency complicated by other diseases. Therefore, it is necessary not only to confirm the presence of thiamine deficiency, but to ascertain the improvement after thiamine therapy, to make sure the diagnosis is correct.

II. Effects of Diuretics on Thiamine Metabolism

As reported previously, thiamine deficiency was observed in some patients with congestive heart failure, which we treated with diuretics. In furosemide administered rats, the thiamine concentrations and transketolase activities were lowered and thiamine pyrophosphate effects were elevated in various organs, such as heart, liver, kidney and blood.

To elucidate the mechanism of these diuretic induced thiamine deficiencies, the changes of thiamine levels both in blood and urine were analyzed in 6 patients with congestive heart failure, during furosemide treatment. The blood levels of thiamine were decreased from 5.48 ± 1.82 μg/dl to 4.10 ± 0.42 after 1 week and 2.89 ± 0.79 after 2 weeks. The urinary excretions of thiamine were increased from 8.28 ± 3.85 μg/day to 111.1 ± 64.6 after 1 day, 85.8 ± 35.8 after 1 week and 98.6 ± 47.8 after 2 weeks, in accordance with the lowering of blood thiamine levels.

Thus, the observed thiamine deficiency after diuretic therapy is considered to be mainly due to the augmented urinary excretion of thiamine. It, however, did not occur in all the cases treated with diuretics, but was found chiefly in the patients not taking a proper diet for their reduced appetites.

How does such a thiamine deficiency affect the hemodynamics of congestive heart failure? Does an obvious improvement occur after adequate thiamine administration? To our regret, we are not able to answer to these questions at present. However, considering the importance of thiamine in energy metabolism, its depletion should not be neglected. Therefore, careful consideration is required in the treatment of patients where long-term diuretic therapy is inevitable.

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