Chapter 9

BERIBERI

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CONTENTS

Introduction

Beriberi, which is caused by thiamine deficiency, was once a major disease problem in many parts of the developing world characterized by a predominantly rice-based diet. Today, the prevalence of beriberi has been greatly reduced although it remains endemic in a moderate or mild form in certain areas, and periodic outbreaks are reported in times of crisis. Even in the developed countries, beriberi, or more often Wernicke's encephalopathy, is seen in alcoholics, who have a low level of thiamine intake. With the falling prevalence of beriberi, the relative proportions of adult and infantile cases have altered, the latter becoming more predominant; it is interesting to note that adolescent beriberi has not been frequently described. The predominant manifestations of beriberi appear to vary from area to area and from time to time and perhaps depend on the severity and chronicity of the deprivation and possibly also on the co-existence of other factors (the effects of alcohol as well as thiamine deficiency in the alcoholic, for example). Numerous classifications of different types of beriberi have been described in the literature but no attempt is made here to categorize these types. Detailed descriptions of the effects of thiamine deficiency are given in various reviews (*1, 2, 9*) and the history of beriberi has been described by Aykroyd (*3*). Shimazono & Katsura (*4*) have prepared a detailed bibliography of the Japanese literature.

Clinical Manifestations

Adult beriberi

Clinically, dropsy is one of the important signs and is usually present in early stages of the disease. In mild cases it is demonstrable only slightly over the pretibial area; however, even in such cases, oedema is present in the calf muscle and tenderness is elicited by gripping. As oedema increases in intensity the entire lower extremities and the face will become swollen. In a proportion of cases, often those occurring in older patients or alcoholics, beriberi may develop without evident oedema and the neurological lesions (including a wasting of muscles) may predominate. The clinical difference may be due to differences in the chronicity and severity of the deprivation.

Cardiovascular symptoms are frequent. In early stages the patient will have palpitation on exertion or mental excitement, and when the disease has advanced palpitation and dyspnea will occur even at rest. The limit of the cardiac dullness shifts to the right at the beginning and then to the left. Enlargement of the cardiac dullness upward is usually minimal. If the cardiac enlargement becomes marked there is visible epigastric heart thrust. X-ray examination will corroborate the finding that the heart is enlarged to both sides but particularly to the right. Orthodiagraphic studies will reveal marked displacement of the heart with changes in body position and demonstrate exaggerated downward displacement in the standing position and a sideways displacement in the lateral position.

Although the majority of mild to moderately advanced cases show no demonstrable changes, the following alterations have been observed in those who have marked cardiovascular symptoms: high P and QRS waves, abnormal T waves, prolongation of PQ intervals, ventricular preponderance, and myocardial damage. Arrhythmia is rare and mostly of sinus origin on account of vagotonia.

The pulse is usually rapid but slow in isolated cases. Such bradycardia is unstable and the pulse rate readily increases after slight exertion. The pulse is large in size and rapid. The sphygmogram shows steep peaks with a sharp rise and fall and, frequently, an elastic rebound immediately follows and is typified by a dicrotic pulse. Low diastolic pressure, usually below 60 mm Hg, has been recognized widely as one of the most characteristic signs. The diastolic pressure falls while the disease is still in its earliest phase and very often reaches zero in moderate to severe cases; the systolic pressure is not much altered.

The state in which the beriberi patient has developed acute heart failure has been termed "Shoshin"; a characteristic clinical picture is presented. The pulse is rapid, usually more than 120 per minute, and large in size. The diastolic pressure drops and is sometimes as low as zero with audible arterial sounds. The heart is enlarged to both sides, more pronouncedly

to the right; heart sounds are intensified and slight murmurs are often heard. The lungs show signs of congestion; the liver is enlarged; the abdomen is distended; and the patient is nauseated and vomits. Cyanosis may be noted in the face and oedema sometimes develops suddenly. Urine output is decreased, and protein and coma casts (renal casts containing strongly refracting granules that are said to indicate oncoming coma in diabetes as well as beriberi) may be found. Consciousness is not lost at any time and the patient tosses about in agony, finally succumbing. Shoshin is more frequently observed in beriberi of otherwise healthy men but is occasionally seen among pregnant women and women in the lactating period after delivery. The onset is sudden and follows excessive fatigue or intemperance.

The neurological signs constitute one of the beriberi triad and are evident even in the early stages. Polyneuritis and paralysis of the peripheral nerve predominate; the central nervous system is scarcely involved. Manifestations are seen in the autonomic, sensory, and motor systems. The autonomic nervous system is functionally altered in the early course of the disease, as the clinical and pharmacological findings in beriberi patients suggest.

In the sensory system, tactile sensation is first affected, then there is pain, and finally temperature sensitivity is altered. By the time all these sensations have been diminished, deep sensation begins to be disturbed. The sensory disturbances are usually not so marked as to be termed "anaesthesia", but superficial hyperaesthesia is more or less characteristically distributed, beginning in the lower extremities, finger tips, lower abdomen, and perioral areas and gradually expanding. The sensory effects are usually symmetrical although the side that is in greater use tends to be affected first. Paraesthesia is often the earliest sign of diminished sensibility and the patient complains of a burning sensation in the legs and toes. Although rare, sensory disturbances of the oral cavity are encountered in a few cases.

Paralysis of the motor nerve occurs after the sensory disturbances. This also begins in the tips of the lower extremities, then in the fingers, and ascends progressively. In infants, it sometimes starts in the vocal cord. In the lower extremities, motor palsy begins from the toes and dorsal flexion becomes difficult because of the involvement of the peroneal nerve. The patient is liable to stumble when walking. If paralysis further involves the muscles of the thigh, gait is difficult and the foot becomes contracted to assume the form of the so-called pes equinovarus. In the upper extremities, paralysis begins from the fingers and ascends involving the extensors earlier and more seriously than the flexors; so-called claw-hand may develop.

The tendon reflexes in beriberi become hypoactive, first in the Achilles and then in the patellar tendons; a loss of the knee jerk with intact Achilles tendon reflex is unusual. Loss of deep tendon reflexes of the lower extremities sometimes appears before demonstrable sensory damage. However, the loss of the triceps and periosteal reflexes is usually preceeded by sensory disturbances in the upper extremities.

Frequently, vertigo and instability of the body during walking are noted in beriberi patients. The shaky gait is equivalent to positive Romberg's sign and mostly caused by impaired vestibular function in advanced cases although it is partially due to decreased deep sensations. Nystagmus, as a sign of manifestation of vestibular malfunction, has been reported to occur particularly in alcoholics who develop Wernicke's encephalopathy.

Biochemically, the patient with beriberi exhibits a very low excretion of thiamine in the urine, reflecting the low dietary intake. Blood levels are also reduced. Measurement of red cell transketolase (2.2.1.1.) activity (and the magnitude of the *in vitro* response to added thiamine pyrophosphate, an essential coenzyme) has been suggested as a diagnostic aid. In severe cases, there is evidence of an impairment of glucose metabolism, and pyruvic and lactic acids tend to accumulate in the blood, particularly after a glucose blood test.

Infantile beriberi

Beriberi in infants has been a major problem in some areas of the world. Clinically it is particularly significant since the onset of readily apparent symptoms is often very rapid and the fatality rate is very high; death often occurs within a few days of the onset of detected symptoms. It is apparently a very acute form of the disease; chronic beriberi, which may be present in the adult, is seldom seen in the infant. Beriberi infants are, in general, pale, oedematous, and ill-tempered. The symptom that is most frequently found in infantile beriberi and seldom seen in adult beriberi is gastrointestinal disorders such as loss of appetite, vomiting or milk diarrhoea, and green faeces. Vomiting of milk occurs repeatedly several times a day, and in severe cases beriberi infants even vomit a coffee-grounds-like mass. It is now confirmed that a prolongation of the time of transfer of milk from the stomach to the small bowel is one of the reasons for the vomiting of milk. Next to these reactions the characteristic symptom of infantile beriberi is hoarseness. It is observable in a high proportion of cases and may be seen before there is any sign of paralysis of other nerves. In many cases blepharoptosis is also seen. In most cases of adult beriberi the development of paralysis starts from the peripheral nerves, whereas in infants with beriberi paralysis occurs in the area of the cerebral nerves. As a rule, knee and ankle jerk hypoactivity is observed in infantile beriberi, especially in the advanced stages of the disease.

In infants suffering from somewhat advanced beriberi the facial expression is apathetic and these infants become incapable of fixing the head. Body positioning and grasping power also become weak. In more severe cases, convulsion followed by comatous states is seen; the condition therefore suggests a diagnosis of encephalitis or other disease of the central nervous system. The specific lesions in such disorders are not defined. The

cerebrospinal fluid of these infants shows no significant changes in transparency, cell number, sugar content, or other chemical properties, but an increase in globulin and the acetone content can be observed at times.

Symptoms and signs involving the cardiovascular system are seen in infantile beriberi in a degree similar to that in adult beriberi, with the exception that there is a higher incidence of tachycardia in infants. Next to tachycardia, dilatation of the right ventricule, accelerated cardiac rhythm, and a marked accentuation of the second pulmonary sound are found. In some infants, systolic murmur is audible at the cardiac apical region. Diastolic pressure is decreased and the vascular murmur can be heard. Such circulatory disturbances give rise to a sudden shoshin state by a trivial event, particularly a slight infection of any kind. Moreover, the liver and the spleen become enlarged and palpable on account of congestion resulting from cardiovascular impairments.

Epidemiology

Beriberi is a characteristic disease of rice-eating communities associated particularly with the consumption of polished rice. It is rarely seen in rice-eating communities where the rice is either "parboiled", which is a common practice in India, or "undermilled". These observations have been explained on the basis of the thiamine content of different types of rice. Clinical and experimental studies have suggested that the development of clinical manifestations of beriberi requires an intake of thiamine below about 0.2 mg per 1 000 kcal (0.05 mg/MJ); biochemical signs may be present at intake levels as high as 0.3 mg/1 000 kcal (0.07 mg/MJ) (*5*). A high carbohydrate, low fat diet may increase the requirements slightly. Both of these conditions are fulfilled by most varieties of polished rice. However, the thiamine content of the aleuron layer of rice is relatively high. By leaving this layer partially or completely intact (as in undermilling) or solubilizing the thiamine and making part of it migrate into the endosperm (as in parboiling) the thiamine content of the food is kept above the critical level for the production of clinical signs of deficiency. The effect of the introduction of polished, instead of parboiled, rice in Malaysia was well described by Burgess (*1*) and has also been documented for Japan (see below). Less often, beriberi has been noted in populations dependent almost entirely on refined wheat flour.

Beriberi tends to disappear as economic conditions improve and diets become more varied. It is seen periodically in times of emergency, in military campaigns, expeditions, etc. Here again, the cause can be ascribed to severe restriction of the range of available foods and dependence on rice as the major source of energy. Sporadic cases are seen among alcoholics in almost all countries; alcohol-derived energy displaces food without providing the thiamine required to metabolize the ingested sources of energy.

As the prevalence of clinically apparent beriberi fell in adults in many places health workers were surprised to note that it remained a problem in breast-fed infants. Epidemiological studies have demonstrated that the syndrome is still attributable to thiamine intake. The thiamine content of breast milk of even well nourished mothers is low, although apparently quite adequate for the normal breast-fed infant (*5*). However, the thiamine concentration of milk varies with intake. Examinations of mothers of infants with beriberi have revealed that most show some symptoms suggestive of thiamine deficiency and all have low dietary intakes; they may be said to be suffering from "subclinical" thiamine deficiency and are producing milk that is definitely inadequate in thiamine concentration though possibly quite adequate in volume and concentration of other nutrients.

Table 1. Number of deaths and death rates due to beriberi for selected years [a]

Year	Total number (A)	Number of infants (B)	B/A (%)	Death rates per 100 000 population
1900	7 180	544	8	15
1905	11 703	2 129	18	25
1910	9 598	3 182	33	19
1913	5 633	1 868	33	11
1920	14 239	5 856	41	25
1923	26 796	11 373	42	46
1928	19 036	9 582	50	30
1930	15 419	7 897	51	24
1935	10 062	5 767	57	14
1940	7 179	4 437	62	10
1950	3 952	2 482	63	5
1955	1 126	616	55	1.3
1959	447	192	43	0.5

[a] Source: Inouye & Katsura (*6*).

The history of beriberi in Japan illustrates a number of the points about the epidemiology of this disease. The incidence of deaths from beriberi in Japan since 1900 is shown in Table 1; the drop after 1930 is readily apparent. The table also illustrates the change in pattern from adult to infantile beriberi, probably attributable to a more rapid decline in the fatality rate in adults than in infants. As illustrated on Table 2, there was a marked difference in mortality rates between urban and rural populations in the early part of

Table 2. Death rate for beriberi in urban and rural communities [a]

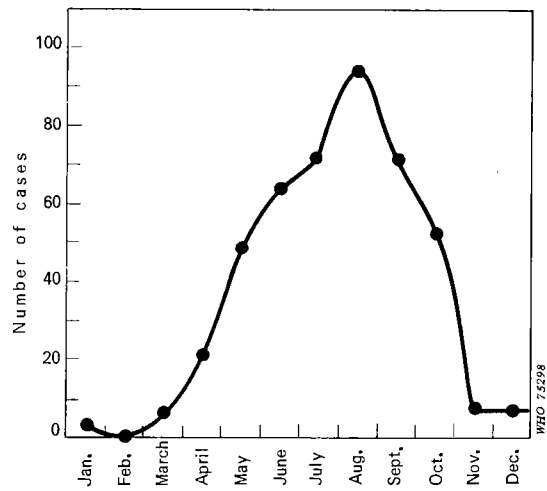
Year	Urban [b] (rate per 100 000 population)	Rural (rate per 100 000 population)
1913	36	8
1920	70	20
1930	32	19
1935	20	13
1948	7.8	7.8

[a] Source: Inouye & Katsura (*6*).

[b] Six cities (Tokyo, Kyoto, Osaka, Nagoya, Kobe, and Yokohama).

this century. This probably reflects the greater use of polished rice in the urban areas. Marked seasonal variations were evident in the early part of the century although by 1940 these differences had largely disappeared. A similar seasonal difference, reaching a peak in August, was seen in morbidity from infantile beriberi (Fig. 1).

Fig. 1. Monthly frequency of infantile beriberi in Japan [a]



[a] Data from Matsuyama (*8*).

Morbidity data are available for Japan at periodic intervals. In 1940, based upon life insurance statistics, the prevalence was reported to be 12.9% (males 10.3%, females 15.4%). In a study of infantile beriberi between 1903 and 1922 the ratio of cases in males and females was 1.76 : 1 and peak mortality was seen in infants aged 2–4 months. A survey of patients visiting the clinic of the Tokyo Medical and Dental College in 1951 revealed a prevalence of 29% who had at least two of the major signs of the disease—namely, hyporeflexia, hypesthesia, oedema, lowered diastolic blood pressure, or tenderness upon grasping the calf muscle. In recent years typical beriberi symptoms have become very rare and a precise estimate of present prevalence is not available, though this may be forthcoming from the current National Nutrition Survey conducted by the Ministry of Health and Welfare. The frequency of observation of hyporeflexia and oedema still seen in Japan (Table 3) suggest that thiamine deficiency, perhaps in a subclinical form, still persists.

Table 4 shows the incidence of beriberi among armed forces personnel. In both the army and navy morbidity and mortality rates were high up to 1883–84. Since then, there has been a gradual decline as a result of improvement in food quality. This table also documents the relationship between

Table 3. Frequency of hyporeflexia and oedema [a]

Year	Hyporeflexia (%)	Oedema (%)
1950	8.0	1.2
1951	7.0	1.1
1952	7.3	2.0
1953	7.4	1.7
1954	7.5	1.8
1955	6.8	1.5
1956	9.1	2.8
1957	10.5	2.6
1958	9.5	2.8
1959	10.9	2.7
1960	9.1	2.7

[a] From the National Nutrition Survey conducted by the Ministry of Health and Welfare, Japan.

Table 4. Incidence of beriberi in the Japanese armed forces in peacetime [a]

Year	Army		Navy	
	Case rate (%)	Death rate (%)	Case rate (%)	Death rate (%)
1878	37.0	1.1	32.8	2.1
1879	25.5	0.6	38.9	2.8
1880	17.1	0.3	34.8	1.5
1881	16.1	0.4	25.0	2.5
1882	19.5	0.5	40.5	2.6
1883	24.1	0.6	23.1	3.9
1884	26.4	0.6	12.8	1.1
1885	14.3	0.15		
1886	3.5	0.10		
1887	4.9	0.16		
1888	3.7	0.13		
1889	1.5	0.08		
1890	1.0	0.06		
1891	0.5	0.01		
1892	0.1			
1893	0.2	0.04		

[a] Data from Shimazono (7).

morbidity and mortality in thiamine deficiency. With diagnosis and treatment, recovery rates for adults are good. In the absence of adequate treatment, fatality rates are believed to have been high. Periodic outbreaks of beriberi are associated with the food stringencies of military campaigns; this is well documented in Table 5. It is also apparent that after the discovery

Table 5. Incidence of beriberi in the Japanese forces in wartime

Year		Case rate (%)
1894–1895	(Sino-Japanese War)	25.4
1904–1905	(Russo-Japanese War)	20.5
1914	(First World War)	3.3
1928	(Tsinan incident)	2.1
1931–1936	(Manchurian incident)	0.6
1940–1945	(Second World War)	unknown

of thiamine and its role in the etiology of beriberi control measures were highly effective in the prevention of major outbreaks of beriberi. The higher prevalence of beriberi in navy personnel by comparison with army personnel (Table 4) was probably also attributable to increased dependance upon rice during sea voyages.

The existence of an enzyme, "thiaminase", capable of destroying thiamine has been reported in several species of fish; heat lability varies with the type of fish and shellfish. Some authors have suggested that destruction of thiamine by this enzyme may be involved in the etiology of beriberi in man (it is significant in animal husbandry); however, the epidemiological evidence is not clear. Thiaminase could only play a role if fish containing the active enzyme were mixed with the thiamine-containing foods and allowed to stand for some time before consumption.

Treatment and Prevention

The specific treatment for beriberi is the administration of thiamine. Prior to the isolation and synthesis of thiamine, the feeding of rice bran (or bran extracts—"tikitiki") was demonstrated to be an effective treatment; mild cases respond to a mixed diet. Today, however, the preferred treatment is crystalline thiamine and an adequate diet. Experience in Japan has suggested that the therapeutic regimen for beriberi should be as follows: during the initial week, about 10 mg of thiamine per day; for several subsequent weeks, 3–5 mg/day; thereafter, a maintenance dose of 1–5 mg/day. It has become customary to administer the thiamine parenterally in the initial weeks and then to give the maintenance doses orally. In severe beriberi, particularly of the fulminating type of cardiovascular beriberi (shoshin), initial dosages of 50–100 mg of thiamine should be administered intravenously or parenterally. With this type of treatment response is usually very rapid in the initial stages although some time may be required for complete recovery of some of the manifestations. Nursing mothers with signs of latent or mild beriberi should be treated as described above if the development of acute beriberi in the infant is to be prevented.

In the community there are several possible approaches to the prevention of beriberi. Diversification of the diet or encouragement of the use of parboiled or undermilled rice are logical approaches, though not always feasible or acceptable in practice. Fortification of rice is technologically feasible and, particularly in areas where rice is centrally milled, has proved to be a feasible approach. Even with local milling, it may be possible to add a heavily fortified "premix" to the local rice. Direct supplementation of high risk groups, particularly lactating women, is another approach and is particularly important in combating outbreaks of infantile beriberi. Because the storage capacity of the body for thiamine is limited, the type

of periodic dosing used for vitamin A deficiency is not effective; daily, or perhaps weekly, supplementation is probably necessary. It has been noted that some varieties of rice have higher thiamine contents. Introduction of these varieties might be considered, but it must be recognized that for rice, perhaps more than any other common food, there are very strong local preferences for varieties having particular cooking properties and flavours.

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