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Review Article

Review of Avitaminosis Fever and Its Clinical Significance

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Abstract

Avitaminosis fever is caused by minimal storage or maximal consumption of B vitamins, especially thiamin, riboflavin or niacin inside human body. They were often found after prolonged ultra-heavy labor and hunger. Berberi fever was most important, not rare and fatal, usually associated with random combinations in a great mess of severe signs and symptoms from multiple organs and endocrine glands controlled by autonomic nervous system causing very queer,. complex, complicated clinical manifestations, which made the diagnosis very difficult and confused. It should be diagnosed collectively as autonomic nervous system dysfunction or crisis, briefly as dysautonomia. The dramatic therapeutic effect of parenteral thiamin on dysautonomia remind people that it may be a very powerful physiologic super antibiotic in eliminating microbial infections regardless pathogen and severity as observed. It may be also a powerful anti-tumor agent and had been successfully tried in cyst, lipoma, osteosarcoma, and lyphoma. Ariboflavinosis fever was milder and commonly found in pediatric especially during winter and spring. It often associated with erythematous patches. Pellagra fever was found in two cases.

Keywords: Ariboflavinosis fever; Avitaminosis fever; Beriberi fever; Common cold; Dysautonomia; Embolism; Furuncle; Pellagra fever; Thromboses; Viral infection

Introduction

Fever is a common clinical sign in many kinds of diseases. The most common cause is malnutrition related infections, such as tuberculosis, pneumonia, or gastrointestinal disorders. Their treatments invariably depend on antibiotics. However, fever could be resulted directly from severe deficiency of some nutrients themselves, such as berlberi fever, ariboflavosis fever, or pellagra fever. They were observed in a population with terribly hard labor and hunger, such as in a labor camp 1958-1962 before and during Nationwide Hunger [1]. This paper introduces the follows: 1. Avitaminosis fevers due to deficiency of thiamin, riboflavin, or niacin themselves might be found in cases with prolonged severe labor and hunger 2. Thiamin deficiency fever was very violent and often involved multiple organs and endocrine glands from different systems and often leading to death. Its diagnosis was very complicated and confused, which could be collectively termed as dysautonomia 3. High dose of parenteral thiamin could surely bring down high fever in avitaminosis fever, however unexpectedly, high fever due to different microbial infections including virus and bacteria or even lymphoma [2] could be normalized with it. Therefore, high dose thiamin injection may be a physiologic anti-microbial agent comparable or superior to the current best antibiotics.

Thiamin deficiency fever

Accidental finding: Mr. GONG KM was a 26-year-old laborer who suffered from frequent cramps and persisting numbness of the extremities for 3 years. After arduous labor for several days, he experienced sudden onset of high fever and severe headache as if hit on the head with a hammer on a day of Feb 1959. He complained also tightening of the chest. The temperature rose to 41˚C even under penicillin from the beginning and followed by herbal medicine. Respiratory difficulty developed and asphyxia resulted as if his chest were bandaged by multiple wide bands. According to the successfully relieving arm moving failure in a carpenter with parenteral thiamin 10 mg, same medicine of same dose was injected. Asphyxia and headache dramatically improved. Surprisingly, the high temperature decreased to 38.5˚C after one hour although it returned to 39.5˚C two hours later. Another 50 mg of thiamin was then injected and the temperature normalized with full clinical recovery. Therefore, thiamin deficiency fever was diagnosed accidentally (Figure 1).

Dysautonomia syndrome: Thereafter, several laborers with high fever had been observed and cured with parenteral thiamin. Their onset were abrupt and the course were rapid. Temperature was usually above 40˚C. The accompanied abnormalities were often the random combinations of "unrelated" severe signs and symptoms of multiple organs and endocrine glands from different systems, including severe headache or coma, severe cardiac arrhythmias such as trigeminy or bigeminy, pulmonary edema, urinary incontinence or polyuria, extensive muscle cramps in the extremities and even the lumbar region, intestinal paralysis manifested as abdominal fully bloating or flatulence, and occasionally massive watery diarrhea. The involvements of multiple system simultaneously made the diagnosis extremely confused and difficult. The appropriate term should be autonomic nervous system syndrome or crisis and briefly, dysautonomia [3].

For example as in case 2, Mr. WANG CZ, an emergency case of 56 years male from other unit, Aug 1959. Suffered from continuous high fever 40˚C for 4 days. The associated signs were fully bloated abdomen as a full termed pregnant woman, polyuria and incontinence, extensive leg cramps. His major therapy was daily 5% glucose intravenous dripping and clinical condition progressed and hypotension appeared. VB1 400 mg was suggested to add into the

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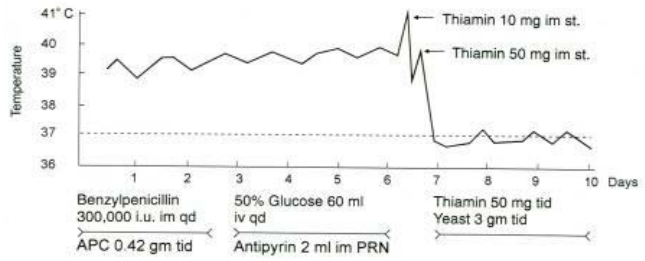

Figure 1: Temperature curve of case 1.

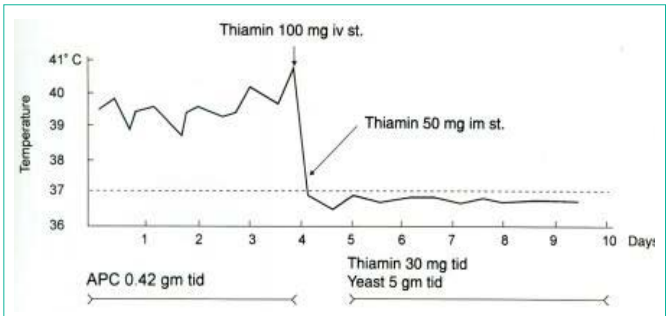

Figure 2: Temperature curve of case 3 several days after Nationwide Hunger.

dripping bottle. All signs including high fever disappeared within one day and fully recovered. His diagnosis should be dysautonomia or ANS system syndrome because of involvement of multiple systems.

The dying case saved while much mild case died: After the announcement of Nationwide Hunger at November 1960, food allocation for each laborer was drastically reduced to 12 kg of corn flour a month or 400 grams (1412 Kcal) a day, which was about 2/5 of the original already inadequate allocation, or something like 1.0-1.5 hamburgers, for an average laborer. Case 3 [2] was 32-year-old Mr. LI SJ. At December 5, 1960, he violated the camp regulation by secretly going out for fishing by broke the ice. He was punished by putting into confinement and reducing food by half, equivalent to 200 gm of corn flour a day. A few days later he experienced increasing weakness, palpitation, shortness of breaths, and severe swelling of his legs. His temperature rose abruptly and was associated with severe headache, nausea, and vomiting. Only APC (aspirin-phenacetin-caffeine) 0.42 could be given 3 times a day. No antibiotics were administered although the temperature fluctuated between 39˚C and 40.0˚C and infection couldn't be excluded. In the afternoon of December 11, 1960, the 5th day of fever, he fell into deep coma. The temperature was 40.2˚C, blood pressure 60/30 mmHg, and bigeminy appeared. Coarse crepitating and rales were heard over both lung fields, which were clear without rales before coma. Intravenous thiamin 100 mg in 50% glucose 60 ml was injected promptly. No antibiotics were available and used. Two hours later, his temperature and heartbeats returned normal, blood pressure 90/60 mm Hg, pulmonary crepitation and rales disappeared, he regained consciousness and moaned, and recovered from possible pulmonary edema as previously believed. Then, he was transferred to a special group with very vulnerable people, actually, candidates of famine death. Their food supply was the same as others; however, homemade liquid yeast was supplied daily. This patient survived and no recurrence (Figure 2).

Shortly, at the same month, December 1960, and same place, a 24-year old laborer was found with fever of 38˚C and a few fine rales were detected at the lower portion of the left lung in the morning. Penicillin G 600,000 IU was injected every 6 hours with an initial double dosage. However, pulmonary rales extended rapidly over both lung fields and he died at the evening within 24 hour due to dyspnea. The comatose case was doomed to die but saved with thiamin, while the much mild case with pulmonary infection died within 24 hours under full dose of penicillin G.

The contrast between these two cases indicated that high dose parenteral thiamin might be a physiologic super-agent against various microbial infections while penicillin completely failed. This observation became a lifesaving suggestion for the following critical case in Tianjin 2016. If confirmed with a large number of cases, regular antibiotics may be replaced inevitably, especially in life-threatening conditions.

Thiamin, a super antibiotic: As inspired by the above cases, high dose parenteral thiamin was used in civil patients with various infections. Therapeutic effect was dramatic as in followings:

Case with fulminating viral pneumonia and thromboses: At the early days of February of 2016, [4] the north hemisphere became bitterly cold. The water pipe inside a building in Tianjin city leaked and icy water flooded down into a resident's bedroom. The 38 years old housewife immediately removed bitter cold water with all her strength and exhausted. Next morning she got fulminating high fever of 40 degree C, a few blood sputum and general pain. On Feb 9, 2016, she admitted to the top Hospital of a University (case No.1007092882) for emergency care. She was noticed on critical and found to have:

a. Severe and unique pneumonia with multiple scattered shadows in both lungs especially the upper portion of the left lung with multiple small perforations. The phylum region in the X-ray film revealed as a large tree with thick and long branches. It was caused by an unknown kind of virus, unidentified when compared with all the specimen in the University.

b. Thromboses in left lateral pelvic, femoral and deep femoral veins of the left extremities and severe edema of the left leg and foot. She was under high risk of embolism.

c. Heart failure.

d. Infection of type C hepatitis.

She received very expensive immunoglobulin, anti-viral, anti-thrombotic and antipyretic medicine daily but no effect for10 days. Mega dose of parenteral thiamin therapy was suggested by this author but rejected by the Hospital. Then her brother secretly carried her home to save her life without contacting the Emergency Department. It was a great joke.

At home, the only treatment was parenteral thiamin 200 mg and an ample of vitamin B complex (containing VB1 10 mg, VB2 2mg, VB3 30 mg, VB6 2mg, pantothenic acid 1 mg) 3 times a day. Body temperature became normal within 2 days and leg edema disappeared within 5 days. Bloody sputum disappeared and she felt well but fatigue and lassitude.

On April 27, 2016, she admitted Beichen Hospital (case No.

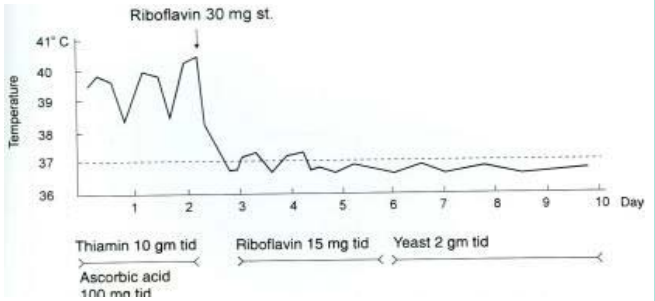

Figure 3: Temperature curve of a pediatric case with riboflavin deficiency fever and rashes.

95442) for check-up and revealed: normal heart, hepatitis C negative, several spot-stripe shadows in the lung phylum especially the left side, few effusion in the left thoracic cavity and few irregular thickness in the left pleura, thromboses were found in femoral and deep femoral veins and no further description. Small perforations in the left lung were not found. Her health became good enough to do household work and injections continued so as to control thromboses and lung infection completely. She was saved.

After 4 months from her escape from the top Hospital, she returned her full job and also worked extra hours to pay the high cost for the hospital. No trouble from thrombosis or embolism had occurred. This should be also studied if thiamin has any effect on thrombosis and embolism. On Dec16, 2016, she was checked again in Tianjin People's Hospital (#0004663770). Her blood count, ECG, and X-ray film of the chest were normal.

A large furuncle: A 38 years old female suffered from a large furuncle at the gluteal region, Nov17, 2018. Its red, hot, severe pain and tender area was about 10 cm. Thiamin 300 mg twice a day were injected. After the third injection, severe pain vanished. It was completely cured without pus formation after 8 injections.

Common cold: Thiamin 200 mg and VB Co.1 ampule were injected for 10 adult cases with common cold in Tianjin west, 2017. Temperature and symptom became free in 1 day for 1 case, 2 days for 5 cases, and 3 days for 4 cases.

Riboflavin deficiency fever

Ariboflavinosis fever was commonly found among young children in winter and spring. It was accompanied by the overt signs and symptoms of ariboflavinosis and other nutrient deficiency. Therapeutic effect of antibiotics was poor in such pediatric cases with fever and riboflavin deficiency. After addition of riboflavin, high temperature became normal promptly. Therefore, riboflavin was carefully tried for confirmation in a 3-year old boy with advanced riboflavin deficiency from a poorest family in the camp. Antibiotics were kept in hand for imminent condition but not used. He was admitted with anorexia and restlessness. The tongue was red. His lips were dry and chapped with typical bilateral angular stomatitis. There was a circular congestive area on the ocular conjunctivae immediately around each cornea. After admission to the clinic, these signs worsened and erythematous patches of varying sizes and shapes developed, first around the eyes, then over the frontal area, the neck, the thorax, and the upper extremities. When placed a finger tip gently on the child skin any where for about 1 minute, a red finger tip shaped patches was formed and stayed about one hour.

He refused to eat and became febrile. No inflammation was observed in the throat. His heart, lungs, and abdomen were normal.

Thiamin 30 mg and ascorbic acid 300 mg were administrated daily. Aspirin was given 50 mg three times a day and occasionally antipyrin was injected. When the temperature reached 40.2˚C, oral riboflavin 30 mg was only used to replace all medicine. Two hours later he became quiet and fell asleep with the temperature dropping to 38.2˚C. Thereafter, riboflavin was given 15 mg three times or two times a day and he became afebrile and free from rashes within 7 days. This case revealed that vitamin B2 deficiency could cause fever and erythematous patches. If parenteral riboflavin were available, the result would be much better (Figure 3).

Pellagra fever

Pellagra fever was observed in 2 advanced cases with severe diarrhea and extensive dermatitis involving the feet, the legs,and the hands. Their temperature returned normal from 38-39˚C. simultaneously with correction of dermatitis and diarrhea after niacin and yeast therapy without antibiotics. In one case, repeated cultures of the exudates from dermal lesions of the legs were normal floras. Clinical response to niacin therapy was much longer than those of thiamin and riboflavin.

Discussion

Review of avitaminosis fever

In 1958, Yamashita [5] observed slight rise of temperature in 20 out of 23 patients with beriberi. At 1959 in the camp, fatally severe fever due to thiamin deficiency was accidentally found. It was then confirmed with several more cases thereafter involved with multiple organs of different systems. Their clinical manifestations were extremely "disordered" or in a great mess and could be collectively categorized as autonomic nervous system crisis or fatal dysautonomia.

As an extension, the clinical response of the dying case of hunger in the December of 1960 became a life saving suggestion for a critical case of viral pneumonia with multiple perforations and thromboses in 3 major veins. This reminded people that parenteral thiamin mighty be a universal physiologic anti-infectious agent or a super antibiotic. Its effects on thromboses and embolism should be also further studied.

In recent years, some cases with Wernicke's encephalopathy associated with fever were reported. It appeared that beriberi fever couldn't be excluded in their cases [6]. Patient with hyperemeisis gravidarum and fever of 38.5˚C reported by Indraccolo et al [7], and 6 out of 9 pediatric patients with Wernicke's encephalopathy and fever reported by Fattal-Valevski et al [8]. However, the relationship between fever and thiamin in their cases had never been discussed.

Until currently, no report had been found about ariboflavinosis fever and pellagra fever. Riboflavin and niacin are very effect in eliminating mucus membranous, nervous, and cutaneous lesions, a very important area for mediccal research. For example, niacin was essential in cure insomnia. Cases of fever due to deficiency of vitamin D and vitamin B12 had been reported recently [9].

Mechanism of avitaminosis fever

This is a great puzzle and remains obscure. The following basic physiology may be helpful in hypothesizing the pathogenesis:

a. Since body temperature is regulated by the hypothalamus [10], one could postulate that local thiamin depletion in the hypothalamus might be responsible for beriberi fever. The decline in thiamin, thiamin phosphates, and thiamin-dependent enzymes could exaggerate oxidative stress and lead to neurodegeneration [11]. Therefore, dysfunction of hypothalamus might cause fever.

b. Riboflavin is converted to Flavin Mononucleotide (FMN) and Flavin Adenine Dinucleotide (FAD), which are cofactors of complexes I (NAD) and II (NADP) for either donating or accepting hydrogen ions in vital oxidation-reduction reaction. Niacinamide or niacin is a precursor for both Nicotinamide Adenine Dinucleotide (NAD/NADH) and nicotinamide adenine dinucleotide phosphate (NADP). Riboflavin and niacin or niacinamide are essential components in coenzyme I and coenzyme II involved in a wide variety of intermediary metabolism including oxidation-reduction reactions [12]. Therefore, metabolic disturbances in peripheral tissues might be responsible for fever in riboflavin or niacin deficiency.

c. Nitric Oxide (NO) was reported as a peripheral and central mediator in body temperature regulation [13]. In malnutrition, nitric oxide synthesis might be poor due to possible deficiency of its building materials including arginine, riboflavin, niacin, iron, and calcium. Endothelial NO synthase is an NADPH-dependent oxygenase that required FAD and FMN as cofactor [14]. Hypothetically, one of the consequences of the suspected NO deficiency in malnutrition might be regulation failure of body temperature, such as high fever.

Therapeutic effect of thiamin on infections

The synergism between malnutrition and infection was clarified until 1960's by Scrimshaw [14]. Exhaustive exercise and malnutrition could be associated with substantial production of reactive oxygen species. Immune responses thereby might be impaired and the susceptibility to infection might increase including [15-18]: a. Signs of inflammation: release of cytokines, activation of immunocomponent cell lines, complement, and induction of acute phase reaction. b. Signs of immunosuppression: decreased T and B cell function, impaired cytotoxic activity, and impaired phagocytic activity. These were the primary theoretic bases for thiamin therapy on infection. A large amount of new theories have been developed but cannot be described here with.

Conclusion

1. Beriberi fever may be not rare. It may be associated with very complicated severe signs and symptoms from multiple organs, endocrine glands of different systems often leading to death as in dysautonomia.

2. Parenteral thiamin was dramatically effective for beriberi fever and might be also a super antibiotic for microbial infections or even some cancers.

3. Thiamin might be a great helper in solving thrombosis and embolism.

4. Ariboflavinosis fever and pellagra fever should be also studied.

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