

# Preface

The past 20 years have seen remarkable advances in neuroscience, neurology, imaging techniques, and diagnostic strategies. These advances have been successfully applied to many different diseases, including thiamine deficiency and associated clinical disorders. Syndromes such as beriberi, Wernicke's disease, Leigh's disease, African Seasonal Ataxia, and various inherited ataxias have all benefited from improved scientific approaches. It is timely therefore to examine new knowledge related to the effects of thiamine deficiency on organ systems and to specific thiamine-related clinical disorders.

The elucidation of the biochemistry of thiamine took many scientists many years to complete and is inextricably linked to the study of thiamine deficiency. Thiamine (vitamin B1) is a water-soluble compound which consists of a pyrimidine nucleus and a thiazole ring. A key derivative of thiamine is thiamine pyrophosphate (TPP), called cocarboxylase. This form is a coenzyme which participates in the decarboxylation of several essential intermediates involved in carbohydrate metabolism. ATP is involved in the transfer of phosphate to thiamine. The two key decarboxylation reactions are the decarboxylation of pyruvic acid and of alpha-ketoglutaric acid. The enzyme transketolase is another enzyme requiring TPP as coenzyme. This enzyme is important in the hexose monophosphate shunt. The dietary requirement for thiamine is based largely on the caloric intake, and primarily that of carbohydrates. Thiamine is widely distributed in plants and animal tissues and is found in high concentrations in yeast, beans, wheat germ, oats, ham, soy beans, etc.

Thiamine is a naturally occurring vitamin which has many functions in mammals. An early and frequently studied role of thiamine is its participation as coenzyme in enzymatic functions in energy metabolism. Clinical descriptions of thiamine-related disorders were published many years before the association of their effects to thiamine deficiency. For example, beriberi was first described in medical literature in 1642 by the Dutch physician Jacobus Bontius (some of his writings related to beriberi have been translated and appear in Appendix A). It was many years later before the association between thiamine and beriberi was discovered. The enormous interest in thiamine deficiency and the associated clinical disorders stems from the fact that these represent classical metabolic encephalopathies, and as such are reversible (treatable) when recognized early.

As stated above, thiamine plays an important role as coenzyme in reactions in the tricarboxylic acid cycle and in the hexose monophosphate shunt. Thiamine deficiency produces symptoms which are primarily localized to cardiac and nervous tissues. These symptoms can be rapidly reversed by thiamine administration, which led to the important concept of a biochemical lesion. The term “biochemical lesion” implies a lesion which occurs before morphological lesions, the presence of which may render the disorder less amenable to treatment and reversal.

Thiamine may also play a role in neurotransmission, as well as several other key biochemical pathways. Perturbation of these important metabolic events may also contribute to key neurochemical alterations, and their reversal in thiamine deficiency and associated clinical syndromes. The fact that frequently the symptoms associated with both pure thiamine deficiency and those in human disorders related to thiamine deficiency can be reversed (successfully treated) in early stages is promising. If the biochemical lesion can be recognized and corrected before the onset of less reversible structural changes, recovery and return to normal function is possible.

Clinical disorders shown to be directly related to thiamine deficiency include beriberi, Wernicke’s disease, Leigh’s disease, African Seasonal Ataxia (ASA), inherited ataxias, central pontine myelinolysis, and others.

Pure beriberi heart disease is rare in the United States; however, it is endemic in other parts of the world. The majority of cases of beriberi (85%) are subacute and mild. The remainder of cases may be more severe, and if not treated, death may ensue. Since beriberi is a complicated nutritional disorder, it is not necessarily a disorder of thiamine deficiency alone; however, treatment with thiamine usually reverses symptoms, sometimes in only hours. There is a long, rich history relating to beriberi, including the pioneering work of Christian Eijkman, which resulted in the awarding of a Nobel Prize (Dr. Eijkman’s Nobel Prize speech is reproduced in Appendix C).

Wernicke’s disease, first described in 1881 by Carl Wernicke, occurs frequently in the United States and is usually associated with chronic alcoholism. Like beriberi, Wernicke’s disease is a complicated nutritional disorder, but in the early stages, many symptoms can be reversed by thiamine administration. Wernicke’s disease may have a rapid onset, and neurological symptoms consist largely of confusion, ataxias, nystagmus, and ocular palsies. Other brain stem symptoms may include stupor and coma. Many Wernicke’s patients may lapse into the more chronic disorder, Korsakoff’s psychosis. In later stages, symptoms may be associated with structural alterations in specific brain sites. Classic studies by Dr. Maurice Victor and colleagues on Wernicke’s disease were carried out over many years, and are the basis for many publications in this area.

Leigh’s disease (subacute necrotizing encephalomyelopathy) is an uncommon disease with around 200 cases reported in the literature. This disorder seems to be genetically transmitted. In patients diagnosed with Leigh’s disease, there was found in urine an inhibitory substance which blocked the formation of thiamine triphosphate (TTP). Low levels of TTP were found in tissues of Leigh’s disease patients. This was postulated to be responsible for thiamine-deficiency-like symptoms seen in these patients. Leigh’s disease usually begins to be symptomatic around postnatal

month 6–12 following normal development. There appears lethargy, nystagmus, ataxia, failure to thrive, stupor, coma, and death. The lesions in the brain are usually more widespread than those in Wernicke's disease, but similar. Thiamine levels in Leigh's disease patients' blood and tissue are normal, and thiamine administration does not ameliorate the condition. A test for the inhibitor did not provide a conclusive indication of the presence of Leigh's disease, there being significant false positives and false negatives. Recent studies have shifted away from the inhibitor and examined supposed Leigh's disease patients for genetic defects including those with cytochrome c oxidase deficiency. Leigh's disease may represent one variation of the inherited ataxias. These studies and their ramifications will be described in depth. There are many unanswered questions relating to this fascinating disorder.

African Seasonal Ataxia (ASA) is another interesting recently described clinical entity which presumably has a thiamine-related foundation. This syndrome has been recently described in people who live in Western Nigeria and is characterized by ataxia, tremors, and decreased levels of consciousness. These symptoms occur during the rainy season of July through October. ASA usually follows a large carbohydrate meal. At its peak incidence, ASA can account for well over 70% of hospital and clinic admissions.

Various hypotheses have been advanced to explain ASA; however, strong evidence supports a mechanism related to thiamine deficiency. There is a clinical triad of cerebellar ataxia, ocular disturbances, and encephalopathy usually seen in acute thiamine deficiency. Upon examination of the dietary intake of the low socioeconomic strata of patients, it was found that almost all had consumed significant amounts of roasted silkworm larvae *Anaphe venata*. The availability of these larvae in the marketplace corresponds to the rainy season. The larvae represent a valuable protein source for rainforest people.

The practice of entomophagy in low socioeconomic cultures is accepted. Protein sources are relatively scarce for these people, who subsist largely on carbohydrate-rich diets. Subsequently, it has been shown that there is a thiaminase present in the *Anaphe venata* larvae. During the rainy season, these larvae fall from specific trees, and are gathered and sold in markets. Subsequent consumption of larvae containing a thiaminase by people ordinarily eating carbohydrate-rich diets can explain the rapid onset of symptoms resembling those of thiamine deficiency. As a corollary to this recent description are earlier descriptions of similar outbreaks of thiamine deficiency. There was, for example, the outbreak of the so-called Chastek paralysis, a disorder of silver foxes on a fox ranch in Minnesota. These foxes were fed raw fish and within a few weeks developed ataxia, changes in consciousness, seizures, and death. Pathologically, brain lesions resembled those seen in thiamine deficiency. Subsequent work showed the presence of a thiaminase in the viscera of the raw fish, which had precipitated the disorder.

Inherited ataxias are a group of relatively rare neurological disorders genetically transmitted, which have as a common denominator ataxia and the possibility of successful thiamine treatment. These diverse, yet related ataxias include Refsum's disease and Friedreich's ataxia. This group of disorders has a defect in the enzyme pyruvate decarboxylase. Pathologically, these disorders show mitochondrial damage

in selective brain regions. Treatment regimes include thiamine and ketonic diet therapies.

The disorder called central pontine myelinolysis (CPM) represents one variant almost always associated with some other serious chronic disease. Over one half of the reported cases were associated with alcoholism and Wernicke's disease. As the name implies, the key feature is a pathological lesion consisting of a symmetric focus of demyelination localized at the center of the pons. Microscopically, there is demyelination of medullated fibers. A variation of CPM are cases which, in addition to the lesion in the pons, demonstrate demyelinating lesions in other brain regions including the thalamus, cerebellum, cerebral cortex amygdala, putamen, etc. In spite of the predominance of alcoholism and Wernicke's disease as a feature of CPM patients, there are many instances of CPM in serious disorders not associated with thiamine involvement. The relation between thiamine and CPM therefore remains somewhat unclear.

Marchiafava-Bignami disease is yet another relatively rare disorder, which has been associated with thiamine deficiency. This clinical entity has as its distinguishing characteristic, lesions in the corpus callosum. These lesions lead to specific signs and symptoms, which together with MRI can lead to early diagnosis. Before imaging advances, the diagnosis was almost always made at autopsy. As a result of rapid diagnosis, treatment regimes involving thiamine administration have evolved, and cases of Marchiafava-Bignami disease have been successfully treated.

In summary, thiamine deficiency and associated clinical disorders represent an intriguing area of both basic and clinical investigation. Modern imaging and diagnostic strategies have facilitated the rapid treatment, and potential reversal of these clinical disorders. The fusion of laboratory and clinical knowledge serve as an example of how research can translate to successful treatment. This book is designed to bring together cogent results from both basic and clinical investigation. These data will be of interest to neurologists, internists, nutritionists, biochemists, neurochemists, neuroscientists, and many others with interest in thiamine deficiency. Many questions regarding these clinical disorders as well as thiamine deficiency remain unanswered. We hope this book may serve to stimulate further investigations in these areas.

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