

Wernicke-Korsakoff syndrome

Learning Objectives.

At the end of this module, you should be able to :

1. Understand the causes of Wernicke-Korsakoff syndrome;
2. Describe how thiamine contributes to normal function;
3. Relate how a lack of thiamine contributes to the clinical presentation of Wernicke-Korsakoff syndrome;
4. Recognise the clinical signs presented with this condition, and discuss it's management.

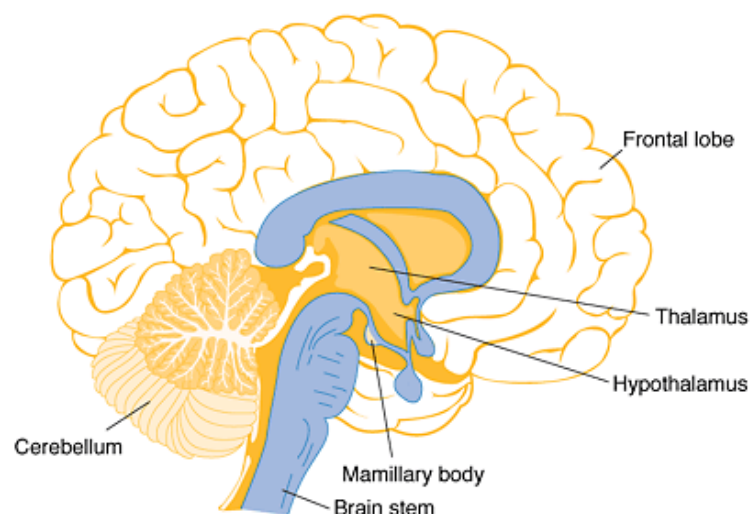
Wernicke-Korsakoff syndrome is a manifestation of thiamine (vitamin B₁) deficiency, usually secondary to alcohol abuse, although there other non-alcohol related causes, such as bariatric surgery, and extreme dietary restriction. The syndrome is a combined manifestation of the short-lived but acute Wernicke's encephalopathy (WE), followed by chronic Korsakoff syndrome. It is generally accepted that WE results from severe acute deficiency of thiamine whilst Korsakoff's psychosis is a chronic neurologic consequence after WE. Approximately 80-90% of alcoholics with WE develop Korsakoff syndrome.

Wernicke-Korsakoff syndrome (WKS) is usually found in malnourished chronic alcoholics, although it is also found in patients who undergo prolonged IV therapy without thiamine supplementation, bariatric surgery, ICU stays, or hunger strikes. In some geographical regions thiamine deficiency has been observed in relation to severe malnutrition, particularly in diets consisting mainly of polished rice, which is thiamine-deficient. The resulting nervous system ailment is known as Beriberi. In individuals with sub-clinical thiamine deficiency, a large dose of glucose (either as sweet food or glucose infusion) can precipitate the onset of overt encephalopathy.

The disorder is characterised by :

Wernicke's encephalopathy	Korsakoff Syndrome
Confusion	Anterograde amnesia (inability to form new memories)
Nystagmus (involuntary eye movement)	Retrograde amnesia (loss of existing memories)
Ophthalmoplegia (impaired eye movement)	Confabulation (false perceptions and memories)
Anisocoria (unequal pupil size)	Hallucinations
Ataxia (lack of co-ordination)	
Sluggish pupillary reflexes	
Coma / death if untreated	

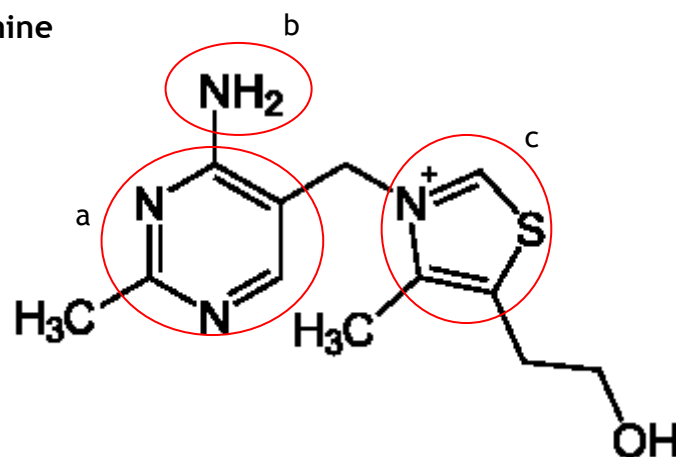
Cerebral damage is a major consequence of thiamine deficiency, the underlying basis of WE. Selective cerebral vulnerability is a major consequence of WE, in which focal areas of the brain exhibit symmetrical areas of profound neuronal loss and accompanying gliosis (proliferation of astrocytes in damaged areas of the central nervous system), occurring most frequently in regions such as the thalamus and mammillary bodies.



WE is surprisingly difficult to diagnose during life, with the classical triad of clinical features of ophthalmoplegia, gait ataxia and a confusional state often being absent in both alcoholic and non-alcoholic cases, leading to only a 20% success rate in valid diagnosis. Evidence from an Australian study suggests that the incidence of WE is higher than anticipated (1.7%), with 88% of these cases being alcohol-related. This suggests a higher incidence than with other disorders such as epilepsy and Parkinson's disease, making WE an important health care issue.

Although acute onset of WE is readily treated by administration of thiamine, neuropathology due to chronic WE can develop following repeated bouts of 'subclinical' thiamine deficiency (TD), suggesting that appropriate intervention during these episodes has the potential to delay or prevent the development of major cell damage. Such intervention is only likely to succeed if the underlying pathophysiology of this condition is well understood, but currently this is not yet the case.

The role of thiamine



The thiamine molecule consists of a pyrimidine ring (a) with an amine group (b) joined to a sulphur-containing thiazole ring (c). In the tissues, thiamine occurs most commonly as the coenzyme, thiamine diphosphate (TDP), in which form it is particularly important for carbohydrate metabolism. TDP serves as a coenzyme for many reactions in carbohydrate metabolism, for example as a complex in the TDP-dependent pyruvate dehydrogenase reaction that generates acetyl-CoA, which is the key source of energy for mitochondrial

oxidation, and an important precursor compound in lipid metabolism.

The polyneuritis which is so often a feature of thiamine deficiency is evidence of specific functions in neural tissues. Acetyl-CoA, produced by the pyruvate dehydrogenase enzyme, is an important precursor of acetylcholine (a neurotransmitter), demonstrating an obvious biochemical link between thiamine, as TDP, and the normal functioning of the nervous system. However, the earliest biochemical studies documented that an abnormality in the oxidative metabolism of glucose, and disruption in energy, supply may underlie many of the neurochemical changes and structural lesions associated with thiamine deficiency. In addition, approximately 10% of the body's thiamine occurs as thiamine triphosphate (TTP) in brain and other neural tissues. The role of TTP remains unclear, although there is some evidence that this form of thiamine is involved in nerve membrane function.

Thiamine status can be assessed using methods which measure thiamine or its metabolites in plasma, erythrocytes and urine. Plasma thiamine concentrations are a reflection of dietary thiamine while urinary thiamine represents the excess of thiamine in the diet above the dietary requirement of the individual. Measuring TDP using the level of saturation of the thiamine-dependent enzymes in erythrocytes provides a functional marker of thiamine status.

There is little surplus thiamine in the body since most is present as active coenzyme in the tissues. Within 10 days of initiating a depletion diet, there is biochemical evidence of thiamine deficiency, and the first physiological evidence (loss of body weight, appetite and other signs) is evident between 21 and 28 days. Previous malnutrition, increased metabolic activity associated with disease and reduced appetite, accelerate the onset of clinical deficiency. The prolonged use of diuretics to treat congestive heart failure, particularly in the elderly, can increase the risk of thiamine deficiency from increased losses of urinary thiamine.

Sources of thiamine

Although thiamine is present in all natural foods, 60-85% of dietary thiamine for people in a large part of the developing world is obtained from either unrefined cereal grains or starchy roots and tubers. Unfortunately, thiamine is removed from cereals by refining and highly milled, polished rice is particularly low in thiamine. Rice which is parboiled before milling retains most of its thiamine since there is inward diffusion of water-soluble vitamins during the process. Other natural sources of thiamine include offal, pork, nuts and legumes but much of the dietary thiamine in Western diets appears in fortified cereals and breads. In the British diet, 45% of thiamine is obtained from white flour products.

Thiamine is water-soluble, therefore it is not present in animal or vegetable oils. Thiamine is stable in slightly acid water up to boiling point but may be leached from food by boiling. Thiamine is unstable in alkaline solution and lost during grain distillation to produce alcohol. Cows' milk is a poor source of thiamine, and additionally further thiamine is lost during pasteurisation.

Two types of thiaminase enzymes are found in food. Destruction of thiamine occurs either by either base-exchange between thiazole and other bases (present in fish, shellfish, ferns and some bacteria) or hydrolytic cleavage of the methylene bridge between the pyrimidine and thiazole moieties (mainly in bacteria). Cooking of food destroys these heat-labile enzymes but food which is not generally cooked, i.e. it is eaten raw or fermented, may lose its thiamine during its preparation or in the gastrointestinal tract. In addition, there also exist heat-stable anti-thiamine factors which are found in ferns, tea, betel nuts and a large number of plants, vegetables and in some animal tissue. These substances generally bind to thiamine, rendering the vitamin biologically unavailable.

Humans require a minimum of 0.33mg of thiamine for every 1,000 kilocalories of energy consumed. Thiamine in food occurs mainly as the di- and tri-phosphates and these are broken down in the gut by phosphatases to release thiamine for absorption. The predominant form of thiamine is thiamine diphosphate (TDP)

which is also called thiamine pyrophosphate and cocarboxylase. The maximum amount of thiamine that can be absorbed from an oral dose is between 2 and 5mg. Thiamine is absorbed mainly from the upper intestine and less thiamine is absorbed on an empty stomach than following a full meal. This could be due to sensitivity of thiamine to alkaline conditions in the duodenum, which are prevented by the presence of food. Absorption of up to 2mg per meal occurs by an active, saturable process involving sodium-dependent ATPase and against a concentration gradient. Some of the newly absorbed thiamine is phosphorylated. A second, passive process of absorption operates at oral intakes of more than 5 mg/day.

This dual mechanism has clinical implications because ethanol inhibits the active but not the passive process of thiamine absorption. Malnourished alcoholic patients exhibit marked reductions in thiamine absorption but alcohol does not block entry of thiamine into the liver nor impair its metabolism in the tissues. Alcohol abuse is likely to block the absorption of thiamine from dietary sources and thiamine supplements are needed to bypass the inhibition and restore a healthy thiamine status. Absorption of thiamine may be reduced in gastro-intestinal disturbances such as vomiting and diarrhoea, ulcerative colitis and neoplasia, and in patients with hepatic disease and achlorhydria (reduced production of gastric acid in the stomach).

As is common in water-soluble vitamins, there is little free thiamine stored in the tissues and most of it is present as active co-enzymes bound to the respective enzymes. Most thiamine in the body is present as TDP (90%) with approximately 10% as thiamine triphosphate (TTP) in the nervous tissues. Particularly high concentrations of thiamine are found in skeletal muscles and in the heart, liver, kidney, and brain. In the tissues, thiamine is required for the assembly and proper functioning of several enzymes that are important for the metabolism of carbohydrates. Proper functioning of these thiamine-using enzymes is required for numerous critical biochemical reactions in the body, including the synthesis of neurotransmitters, production of nucleic acids, and production of fatty acids, steroids, and certain complex sugar molecules. In addition, inadequate functioning of the thiamine-using enzymes can interfere with the body's defense

against the damage (ie, oxidative stress) caused by harmful, highly reactive oxygen molecules called free radicals.

The concentrations of thiamine in specific human tissues are :

- 2-3 µg/g for cardiac muscle,
- 1 µg/g for brain, liver and kidney
- 0.5 µg/g for skeletal muscle.

Thiamine, with some thiamine monophosphate (TMP), circulates in the blood bound to albumin. Thiamine is mainly excreted intact in the urine, but there remain small amounts of thiochrome and other thiazole and pyrimidine metabolites. Urinary thiamine excretion decreases rapidly in thiamine deficiency, indicating that there is a mechanism by which the kidneys conserve it.

The action of thiamine in the cell

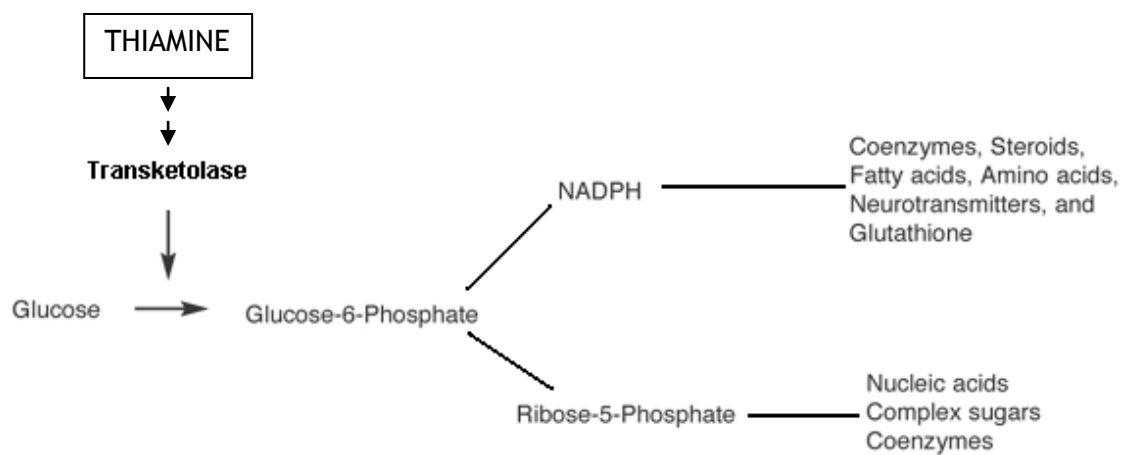
There are three enzymes involved in carbohydrate metabolism which require thiamine as a cofactor;

- transketolase
- pyruvate dehydrogenase (PDH)
- alpha-ketoglutarate dehydrogenase (α -KGDH)

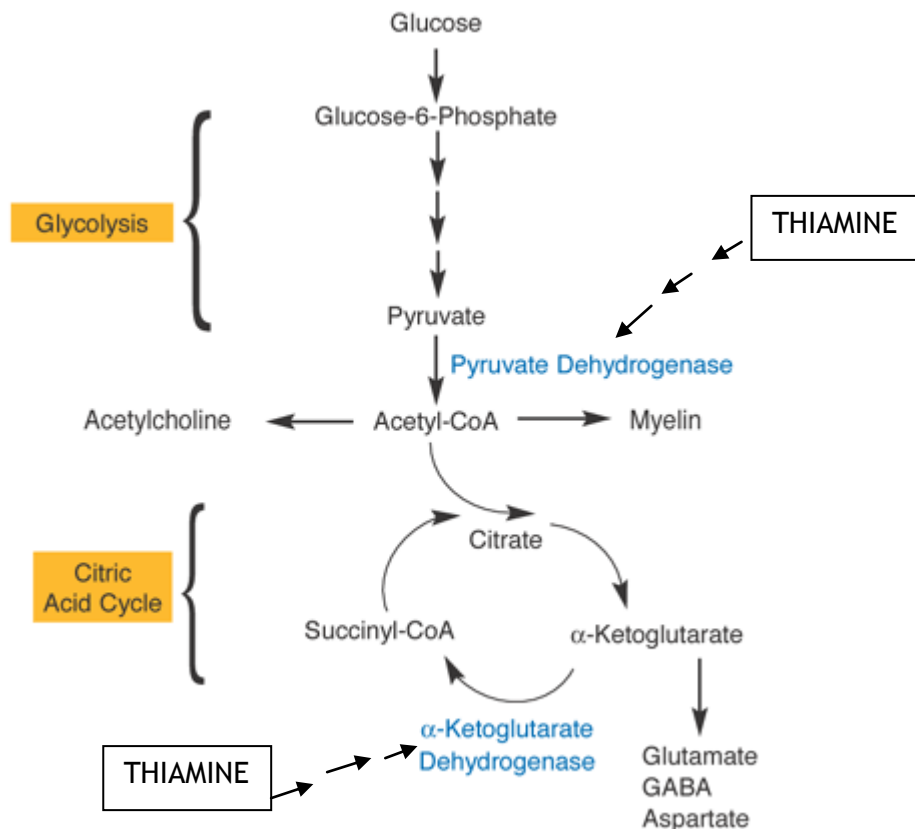
Each of these enzymes consists of several components that must be assembled to yield the functional enzyme, and the addition of thiamine is a critical step in this assembly process. As a result, thiamine deficiency causes reduced levels of functional enzymes in the cell, in addition to interfering with the activity of those enzymes.

Transketolase is an important enzyme in the pentose phosphate pathway. In this pathway, glucose-6-phosphate, derived from glucose, is modified by transketolase, to give ribose-5-phosphate, and nicotinamide adenine dinucleotide phosphate

(NADPH). Both of these molecules are essential for the production of numerous other important molecules in the cell. Ribose-5-phosphate is needed for the synthesis of nucleic acids, complex sugar molecules, and other compounds. NADPH provides hydrogen atoms for chemical reactions that result in the production of steroids, fatty acids, amino acids, certain neurotransmitters, and other molecules. In addition, NADPH plays an important role in the synthesis of glutathione, a compound that is essential in the body's defense against oxidative stress. To function properly, all cells require certain levels of NADPH and ribose-5-phosphate, and the biochemical reaction mediated by transketolase is crucial for maintaining the appropriate levels of both molecules.



The other two enzymes requiring thiamine, pyruvate dehydrogenase (PDH) and alpha-ketoglutarate dehydrogenase (α -KGDH), also participate in different steps of the breakdown and conversion of glucose-6-phosphate through two consecutive chains of biochemical reactions called glycolysis and the citric acid cycle.



The main function of these pathways is to produce adenosine triphosphate (ATP), which provides energy for cellular activity. Decreases in the activities of PDH and α -KGDH can result in reduced ATP synthesis, which in turn can contribute to cell damage and even cell death. In addition, proper functioning of PDH is essential for the production of acetylcholine as well as for the synthesis of myelin, which forms an integral part of the neuron sheath, thereby supporting the conduction of action potentials along the axon and synaptic transmission. The citric acid cycle and α -KGDH play a role in maintaining the levels of the neurotransmitters glutamate, gamma-aminobutyric acid (GABA), and aspartate, as well as in protein synthesis. Thus, the thiamine-using enzymes play numerous vital roles in the functioning of cells, and particularly of neurons.

When thiamine levels decrease, the activity levels of all three enzymes are reduced to some extent. The specific reductions depend both on the enzyme and on the cell type studied, but generally, transketolase activity may be the most sensitive measure of thiamine deficiency, and can be reduced by as much as 80 -

90%. Substantial decline in transketolase activity resulting from thiamine deficiency has been found in various brain areas of alcoholics who do not exhibit the clinical and neuropathological signs of WE, suggesting that thiamine deficiency can cause adverse effects before severe brain damage becomes obvious.

Mechanisms of thiamine deficiency-induced cell damage

Thiamine deficiency can lead to cell damage in the central nervous system through several mechanisms;

1. The changes in carbohydrate metabolism, particularly the reduction in α -KGDH activity, can lead to damage to the mitochondria. Because the mitochondria produce by far the most energy required for cellular function, mitochondrial damage can result in cell death.
2. Disturbances associated with thiamine deficiency in some cell types lead to apoptosis, removing damaged cells.
3. Altered carbohydrate metabolism can lead to a cellular state called oxidative stress, characterised by excess levels of highly reactive molecules called free radicals and/or the presence of insufficient levels of compounds to eliminate those free radicals (i.e., antioxidants, such as glutathione). Oxidative stress can lead to various types of cell damage and cell death.

The effect of alcohol on thiamine uptake and function

Thiamine deficiency in affluent countries clearly is very clearly linked to alcoholism, occurring in up to 80 % of alcoholics, but interestingly only a small number of these go on to develop WKS, and it appears that there are differences between individuals relating to the sensitivity of cells to a lack of thiamine, which may account for this. There are several mechanisms through which alcoholism may contribute to thiamine deficiency, the most important being :

- Inadequate nutritional intake
- Decreased absorption of thiamine from the gastrointestinal tract and reduced uptake into cells
- Impaired utilisation of thiamine in the cells.

Inadequate nutritional intake - Although most people require a minimum of 0.33 mg thiamine for each 1,000 kcal of energy they consume, alcoholics tend to consume less than 0.29 mg/1,000 kcal.

Decreased uptake of thiamine from the gastrointestinal tract - Thiamine must cross a number of barriers, first transferring across the membranes of the cells lining the gut (enterocytes), then enter those cells, and then cross the membranes at the other end of the cells to enter the bloodstream. At low thiamine concentrations, such as those normally found in the human body, this transfer is achieved by a specific thiamine transporter molecule that requires energy. This active transport mechanism appears to be associated with the rapid addition of two phosphate groups by the enzyme thiamine diphosphokinase (TPK) once the thiamine is inside the cell. Acute alcohol exposure interferes with the absorption of thiamine from the gastrointestinal tract at low, but not at high, thiamine concentrations. Animal studies have shown that the activity of the TPK enzyme from various tissues decreased with acute alcohol exposure to about 70 percent of the activity level in control (non-alcoholic) individuals, and with chronic alcohol exposure to about 50 percent. Although no studies have addressed whether alcohol directly affects TPK in humans, indirect analyses have found that the ratio of phosphorylated thiamine (primarily ThDP) to thiamine is significantly lower in alcoholics than in nonalcoholics - that is, that less thiamine is converted to ThDP. This finding suggests that TPK is less active in the alcoholics.

Thiamine malabsorption could become clinically significant if combined with the reduced dietary thiamine intake that is typically found in alcoholics, when other aspects of thiamine utilisation are compromised by alcohol, or when a person requires increased thiamine amounts because of his or her specific metabolism or condition (e.g., in pregnant or lactating women).

Impaired thiamine utilisation - Once thiamine is inside the cells, it is first converted into ThDP by the addition of two phosphate groups. ThDP then binds to the thiamine-using enzymes, a reaction that requires the presence of magnesium. Chronic alcohol consumption frequently leads to magnesium deficiency, which also may contribute to an inadequate functioning of the thiamine-using enzymes and

may cause symptoms resembling those of thiamine deficiency. In this case, any thiamine that reaches the cells cannot be used effectively, exacerbating any concurrently existing thiamine deficiency.

Clinical presentation of WKS

The three components of the classic triad of Wernicke encephalopathy are encephalopathy, ataxic gait, and some variant of oculomotor dysfunction. All three features of the triad are recognised in only about one third of cases.

A high proportion of patients with acute Wernicke encephalopathy who survive develop Korsakoff psychosis, also called Korsakoff syndrome, characterised by retrograde and anterograde amnesia with varying degrees of other cognitive deficits. Wernicke encephalopathy should be considered when any patient with long-term malnutrition presents with confusion or altered mental status. Significant overlap exists between Wernicke encephalopathy and Korsakoff psychosis, in which patients experience delayed and potentially irreversible anterograde and retrograde amnesia. For this reason, the two entities have been described together as Wernicke-Korsakoff syndrome.

Alcohol abuse, AIDS, malignancy, hyperemesis gravidarum, prolonged total parenteral nutrition, iatrogenic glucose loading in any predisposed patient, and other disorders associated with grossly impaired nutritional status have been associated with Wernicke-Korsakoff syndrome.

Numbers of individuals who have undergone weight-loss procedures continue to rise, and post-bariatric surgery patients have a limited capacity for food intake during the initial weeks after a bariatric procedure. Thiamine reserves can be depleted after only 20 days of inadequate supply, therefore, these patients may still present as obese when presenting with Wernicke encephalopathy symptoms caused by thiamine deficiency.

Ocular abnormalities are the hallmarks of Wernicke encephalopathy. The oculomotor signs are nystagmus, bilateral lateral rectus palsies, and conjugate

gaze palsies reflecting cranial nerve involvement of the oculomotor, abducens, and vestibular nuclei. Less frequently noted are pupillary abnormalities such as sluggishly reactive pupils, ptosis, scotomata (an area of diminished vision within the visual field), and anisocoria. The most common ocular abnormality is nystagmus.

Encephalopathy is characterised by a global confusional state, disinterest, inattentiveness, or agitation. The most constant symptoms of Wernicke encephalopathy are the mental status changes. Stupor and coma are rare.

Gait ataxia is often a presenting symptom. Ataxia is likely to be a combination of polyneuropathy, cerebellar damage, and vestibular paresis. Vestibular dysfunction, usually without hearing loss, is universally impaired in the acute stages of Wernicke encephalopathy, but in less severe cases, the patient walks slowly with a broad-based gait. However, gait and stance may be so impaired as to make walking impossible. Cerebellar testing with finger-to-nose and heel-to-shin tests may not exhibit any notable deficit when the patient is recumbent, so it is important to test for truncal ataxia with the patient sitting or standing.

In addition to ophthalmoplegia and ataxia, 80% of adults will have some degree of peripheral neuropathy, which may include weakness, foot drop, and decreased proprioception.

Thiamine deficiency has also recently been shown to possibly cause a gastrointestinal syndrome of nausea, vomiting, abdominal pain, and lactic acidosis. Other symptoms that may occur in addition to, or in place of, the classic triad include vestibular dysfunction, hypothermia, hypotension, and coma. Thiamine deficiency often affects the temperature-regulating center in the brainstem, which can result in hypothermia.

Hypotension can be secondary to thiamine deficiency either through cardiovascular beriberi or thiamine deficiency-induced autonomic dysfunction. Coma is rarely the sole manifestation of Wernicke encephalopathy.

Of patients surviving Wernicke encephalopathy, an important percentage have Korsakoff psychosis, characterised by retrograde amnesia (inability to recall information), anterograde amnesia (inability to assimilate new information), decreased spontaneity and initiative, and confabulation.

Other manifestations of thiamine deficiency involve the cardiovascular system (wet beriberi) and peripheral nervous system (nutritional polyneuropathy).

Wernicke encephalopathy must be viewed as a medical emergency, even if other competing diagnoses of CNS processes are being considered. Because the condition is potentially reversible, early treatment is indicated in patients exhibiting any combination of symptoms and signs, particularly if the patient is in a high-risk population. Onset of the disease may be acute, subacute, or chronic.

Although as little as 2 mg of thiamine may be enough to reverse symptoms, the dose of thiamine required to prevent or treat Wernicke encephalopathy in most alcoholic patients may be as high as greater than 500 mg given once or, preferably, 2-3 times daily parenterally. With a short half-life, multiple daily administrations may be necessary to replete levels and allow for optimal blood-brain diffusions. Ataxia and acute confusional state may resolve dramatically, although improvement may not be noted for days or months.

All poorly nourished patients should be given large doses of parenteral thiamine, particularly if intravenous glucose administration is necessary, even in the absence of symptoms and signs of Wernicke encephalopathy.

Patients with Wernicke encephalopathy are likely hypomagnesemic and should be treated with parenteral magnesium sulfate, as they may be unresponsive to parenteral thiamine in the presence of hypomagnesemia. After correction of hypomagnesemia in conjunction with thiamine repletion, the blood transketolase activity can return to normal and clearing of the clinical signs may occur.

Korsakoff amnestic state

The Korsakoff amnestic state is observed in a small number of patients. Individuals present alert and responsive, but with further examination they demonstrate the

amnesic features of Korsakoff psychosis as the only manifestation of mental confusion. This state appears after the initial confusional state begins to resolve with thiamine administration and persists to some degree in the most severely affected individuals. The Korsakoff state is characterised by both anterograde and retrograde amnesia. Anterograde amnesia is severe but incomplete. This is demonstrated by patients' ability to repeat a series of numbers or objects as they are stated but not able to recall the registered information after 3-5 minutes. Retrograde amnesia is demonstrated by gaps in patients' memories of recent and remote past that antedate the onset of illness. These gaps in memory are what lead to the characteristic feature of confabulation. Confabulation represents filling in of memory gaps with data the patient can readily recall. Debate continues as to whether this action represents a deliberate attempt of patients to hide their memory deficits. In either case, confabulation is seen as a defence mechanism for many patients, as, unless extremely fanciful, the 'filling in' often is highly believable. Confabulation is classically described in Korsakoff dementia, although it may be present in other dementias and is not necessarily present to make the diagnosis.

Prognosis

Administration of thiamine improves disease to some degree in almost all cases, although it is not unusual for neurological deficit and dysfunction to remain. Ophthalmoplegia usually resolves briskly, whilst the initial presentation of global confusion often improves within hours or days. Patients with Wernicke encephalopathy have a significant morbidity and mortality rate, especially if no early signs of neurologic improvement are present after repletion of thiamine. Of patients surviving Wernicke encephalopathy, a percentage will develop Korsakoff psychosis. Typical residual findings from Wernicke encephalopathy include nystagmus, gait ataxia, and Korsakoff syndrome. A worse outcome may be expected in late-stage Wernicke encephalopathy, which is associated with elevated spinal fluid protein levels and diffuse slowing of postsynaptic potentials on electroencephalography. Of patients with Korsakoff psychosis, a significant number do not recover and require long-term institutionalisation. Only about 20% eventually recover completely during long-term follow-up care.

KEY LEARNING POINTS.



1. WKS is a manifestation of thiamine deficiency, usually as a result of chronic alcohol abuse.
2. The disorder is a combination of Wernicke's encephalopathy and Korsakoff Syndrome.
3. Thiamine deficiency is the underlying cause in WKS.
4. Cerebral damage is the major consequence of thiamine deficiency.
5. Thiamine is essential in the production of certain neurotransmitters, as well as myelin. Absence of myelin directly affects neurological function.
6. Thiamine cannot be stored in the body for long periods, and a significantly reduced intake can become problematic within 4 weeks.
7. In situations of chronic alcohol abuse, thiamine levels in the body reduce due to inadequate nutritional intake, decreased absorption from the GI tract, reduced cellular uptake, and impaired utilisation of thiamine by the cells.
8. WKS presents classically as a triad of ocular abnormality (nystagmus being the most common), ataxia, and confusion, although in many cases, not all, or even none, of these may be apparent. In addition, 80% of cases may also present with polyneuropathy.
9. Treatment requires immediate administration of thiamine, in regular doses over multiple days.
10. Korsakoff syndrome can occur subsequent to Wernicke's encephalopathy, and involves anterograde and retrograde amnesia, confabulation, and occasionally hallucinatory episodes.
11. In a significant number of patients, Korsakoff syndrome is permanent, with recovery in less than 20% of patients.