Chapter 3

Wernicke Korsakoff Encephalopathy

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Wernicke Encephalopathy Definition

In 1852, Magnus Huss mentioned a disturbance of memory in alcoholics, arguments that have been then elucidated between 1887 and 1891 by the Russian psychiatrist SS Korsakoff, who considered that the polyneuropathy and the memory disorder represented ‘two facets of the same disease’, which was designated psychosis polyneuritica.

Carl Wernicke described first Wernicke encephalopathy in 1881. He reported a pathological clinical situation, which comprises a triad of symptoms with acute mental confusion, ataxia, and ophthalmoplegia. He described three patients, two with a story of high alcohol consumption and one patient with persistent vomiting that presented with progressive stupor and coma, progressing to death. After this, the classical triad was then deeply described, however, the combination of all three symptoms is only observed in one-third of patients with Wernicke encephalopathy [1].

Therefore, actually, we accept the definition given by general experience, considering the syndrome as an acute neuropsychiatric syndrome, caused by thiamine (vitamin B1) deficiency. Often Wernicke encephalopathy is difficult to diagnose because its clinical symptoms are nonspecific, but delays in treatment can result in coma and death. The disease commonly results from chronic alcohol dependency, anyway non-alcoholic causes are reported in 20% to 50% of patients. Less commonly Wernicke encephalopa-
Encephalopathy may be seen in patients with cancer and malignant lymphoma due to persistent vomit, protein depletion, use of chemotherapeutic agents and malnutrition [2-4].

Other predisposing factors for Wernicke encephalopathy are: a staple diet of polished rice, chronic malnutrition, gastrointestinal surgical procedures, chronic diarrhoea, systemic disease and magnesium depletion.

Alcohol consumption is at special risk for thiamine deficiency because is usually associated with a poor diet and malnutrition, moreover in heavy drinker also compromised thiamine absorption from the gastrointestinal tract, reduced thiamine phosphorylation and impaired thiamine storage is common [5].

As we already said, sleeve gastrectomy (that is continuously increasing in prevalence during last decades) may be related to malabsorptive, restrictive or mixed disorders. Moreover after the surgical intervention hormonal changes (especially regarding the lipoprotein metabolism and glucose metabolism) responsible of thiamine deficiency has been demonstrated, meaning that the effect of this procedure is more complex than it seems to be. Beside the complications due to the surgical procedure (stenosis of the sleeve gastrectomy, anastomotic leak, bleeding or infection) nutritional deficiency and particularly vitamin B1 deficit has been described. All this can lead to Wernicke’s encephalopathy with a 20% mortality rate when it is undertreated [2,6,7].

Similarly an unbalanced diet may be responsible of a thiamine deficiency. In developed countries an increasing number of non-alcoholic cases of Wernicke’s encephalopathy are reported as a result of an extreme diet with fasting/starvation and use of diet pills. Elsewhere the clinical case of an adult woman following a 40-day water-only fasting diet who developed Wernicke’s encephalopathy was described [8,9].

Majchrzak at al studied the B-vitamin status in Austrian population. They found that Vegans presented a significantly lower mean plasma vitamin B(12) concentration than omnivores and vegetarians. As well as the status of riboflavin is considered to be deficient in about 10% of omnivores and vegetarians and in over 30% of vegans. Concluding that Vitamins B(12) and B(2) may need attention in the strict vegan diet [10].

During hospitalization Wernicke’s encephalopathy might occur in patients on prolonged parenteral nutrition [11,12].

Clinical Features

The clinical triad described by Wemicke is composed of ophthalmoplegia, ataxia and disturbance of consciousness and mental state.

Ocular abnormalities are the hallmarks of Wernicke encephalopathy. The oculomotor signs are nystagmus, bilateral oculomotor palsies, and conjugate gaze palsies have
been described. Less frequently pupillary abnormalities, ptosis, scotomata, and anisocoria have been reported.

Encephalopathy is characterized by a global confusional state, disinterest, inattentiveness, or agitation, and delirium (nocument, ideative and persecution delusion).

Gait ataxia is likely to be a combination of pre-existing polyneuropathy, cerebellar damage, and vestibular paresis. Vestibular dysfunction without hearing loss is a common finding. In less severe cases, patients walk slowly with a broad-based gait. Diencephalic sufferance is quite common, due to pre-existing alcoholic polyneuropathy and hypothalamus dysfunction.

Hypothermia is common because of the involvement of the temperature-regulating center in the brainstem. Hypotension, caused by a defect in efferent sympathetic outflow and decreased peripheral resistance, due to autonomic failure and secondary to alcoholic liver disorder, may be present.

Not very frequently, patients survive to Wernicke encephalopathy; among the survivors, there is a large percentage of Korsakoff complex psychosis, characterized by the following: retrograde amnesia (inability to recall information), anterograde amnesia (inability to assimilate new information), decreased spontaneity and initiative, and confabulation. Firstly Korsakoff, a Russian psychiatrist, published different reports describing a syndrome of anterograde amnesia—an inability to form new memories—and confabulation which refers to the practice of filling in gaps the memory by fabricating new memories, in individuals with severe alcoholism or severe starvation.

The symptoms of Wernicke's encephalopathy appear suddenly. The most prominent symptom initially is mental confusion including memory problems. On examination, patients have difficulty moving their eyes to follow a visual stimulus mostly due to external recti deficit. The sufferance might involve the third, fourth or sixth cranial nerves. Moreover, nystagmus that is both horizontal and upright, and paralysis of conjugate gaze can be detected. Pupillary disturbances, ptosis and even funduscopic abnormalities are distinctly rare, thought reported from time to time.

Problems maintaining balance while standing or walking, a condition known as ataxia, are frequently observed as well. If left untreated, most of these symptoms may resolve spontaneously, but the severe memory disorder characteristic of Korsakoff syndrome remains. The typical person with Korsakoff syndrome appears fairly normal on first impression. Intelligence is intact, and individuals with the syndrome can carry on a conversation quite naturally. They are usually able to recall and talk about incidents that took place before the onset of the disorder and recognize family members and old friends without much difficulty. The ability to form new memories is nearly absent, how-
ever. In the course of conversation, people with Korsakoff syndrome may repeat comments or questions several times. They will fail to recognize people they met minutes before or greet a friend with excitement and surprise after a brief trip to another room. These are the characteristics of anterograde amnesia. Research shows that anterograde amnesia results from a failure of memory formation and storage. New information is processed normally, but almost immediately forgotten, never making it into the regions of the brain where memories of the past are stored. People with Korsakoff syndrome thus have no memories of events that happened after the onset of the illness. Many previously stored memories are still available, explaining why individuals with Korsakoff syndrome can usually remember the distant past quite well.

**Mechanism of Damage**

Studies of pyrithiamine-induced thiamine deficiency (PTD), an animal model of Wernicke’s encephalopathy, have in the past failed to directly relate parameters such as thiamine ester depletion [13], thiamine-dependent enzyme changes [14,15], and receptor binding sites [16-18] to the cause of the selective nature of the histological changes that occur in this disorder. Variability between different groups of investigators, in the experimental procedure employed to produce thiamine deficiency over the years has led to differences in the type of model produced, thus complicating attempts to identify the sequela of events that occur during the evolution of the disorder.

In a landmark series of studies, Victor and colleagues reported that examination of the brains of patients diagnosed with Wernicke’s encephalopathy typically reveals gross neuropathological changes that include an increase in the size of the lateral and third ventricles with subventricular regions of the thalamus showing the presence of histological lesions [19]. In the majority of cases, the mamillary bodies sustained considerable damage. Hemorrhagic lesions were present in a small percentage of cases, mostly in the form of petechiae, and were seen most frequently in mamillary bodies as well as the medial, midline and intralaminar nuclei of the thalamus, superior and inferior colliculi, periaqueductal area and floor of the fourth ventricle. Lesions of the cerebellum were reported in approximately one third of cases, with damage localized to the folia of the vermis. It seems quite difficult to obtain adequate information in order to detect previously vermis atrophy due to chronic alcohol abuse or thiamine deficit.

In the thalamus, the most frequently affected region was the medial dorsal nucleus which showed damage in all cases studied. The hypothalamus showed abnormalities in almost all cases with the most prominent lesions in the mamillary bodies. In general, those regions of the brain in close proximity to the ventricular system displayed the most serious histological damage. Loss of neurons was the most obvious abnormality in structures such as the thalamus and cerebellar vermis, with some involvement of fibre
tracts [20]. In addition, brain shrinkage seen in Wernicke’s encephalopathy has been attributed to loss of both white matter and neurons of the cerebral cortex [20-22]. Areas of the brain showing selective vulnerability do not normally share a common origin in embryologic terms [23], and are unrelated in their vascular supply. In affected areas, swelling of astrocytes is often observed with decreases in myelinated fibres and a patchy loss of nerve cells accompanied by activated microglia and reactive astrogliosis. Alterations in the morphology of glia represent the earliest histological changes seen in thiamine deficiency [24,25]. Such changes are suggestive of metabolic changes in these cells which may have an important role to play in the pathophysiology of this disorder.

In a study by Torvik [26], the nature of the neuropathological lesions in patients with Wernicke’s encephalopathy was found to depend on the prominent involvement of the different region of brain. In particular, damage to the mamillary bodies and paraventricular structures of the brainstem was different to that of the thalamus and inferior olives. This study was the first to suggest that two different types of structural lesions occurred in this disorder, and indicates the likelihood of more than one mechanism of brain cell damage in these patients.

Studies of post mortem brain samples from Wernicke’s encephalopathy patients have been limited in number.

In an early study, levels of trace elements were examined by neutron activation analysis in a small group of patients with alcohol abuse exhibiting clinical features of Wernicke’s encephalopathy [27]. Decreases in nearly all elements studied were found in structures with known vulnerability in this disease. Reductions in thiamine-dependent enzymes have been reported in autopsied samples of cerebellum derived from the brains of patients with neuropathological confirmation of PTD [28]. Examination of GABAA receptor binding sites in the cerebral cortex of alcoholics with neuropathologically confirmed WE showed different characteristics compared to control material [29]. Altered gene expression of GABAA receptor subunit isoforms was proposed as a contributing factor [30], although the cause of these differences is unknown. Other studies have demonstrated an alteration of endorphin/thiamine relationships in the brains of Wernicke patients [31], suggestive of a dysfunction of the endorphinergic system.

Although there are several comprehensive descriptions of the neuropathology of Wernicke’s encephalopathy [19,32,33], definitive anatomical substrates for the associated amnesic syndrome, Korsakoff’s psychosis, have not been identified. Cullen et al. [34] have previously shown that the cholinergic nucleus basalis (Ch4) is an exclusive site of neurofibrillary degeneration in thiamine deficient alcoholic patients [35]. The degree of Ch4 cell loss in tightly associated with the memory disorder Korsakoff’s psychosis. The notion that cholinergic deficits can result in memory dysfunction has been extensively evaluated.
in several animal and pharmacological models as well as in neurodegenerative diseases, most notably Alzheimer’s disease.

A role for the Ch4 in memory has been supported in Korsakoff’s psychosis correlating loss of magnocellular basal forebrain neurons to memory dysfunction [36,37].

Cullen et al. [34] demonstrated that in the vicinity of the Ch4, gross morphological changes including forebrain atrophy, ventricular dilatation, and glial scarring disrupted the normal forebrain architecture and gave an irregular concave appearance to the base of the brain in all cases of Wernicke’s encephalopathy. In these cases, the Ch4 nucleus appeared as a narrower, denser band of cells along the basal surface of the brain compared with alcoholic patients without Wernicke’s encephalopathy and controls. Accumulation of lipofuscin pigment was pronounced in all alcoholic patients. Comparison of cell size of Ch4 neurons disclosed no significant difference in the mean cell diameters between Korsakoff’s psychosis, Wernicke’s encephalopathy, alcoholic, and non-alcoholic control groups, even if mean cells diameters could be below in the control group.

There was no significant difference in cell number between alcoholic controls and non-alcoholic age matched controls. The mean number of Ch4 neurons in the Korsakoff’s psychosis and Wernicke’s encephalopathy groups differed significantly from non-alcoholic control groups, with the Wernicke’s encephalopathy mean 24% and the Korsakoff’s psychosis mean 21% below that of controls. These results corroborate earlier reports that cell number remains unchanged in alcoholic patients without Wernicke’s encephalopathy [38]. The data also show that Ch4 cell number is reduced in patients with Wernicke’s encephalopathy both with and without Korsakoff’s psychosis, consistent with our previous finding of neurofibrillary tangles in the Ch4 of alcoholic patients with Wernicke’s encephalopathy [35].

Evidence of cell loss in non-amnesic patients with Wernicke’s encephalopathy, however, refutes previous, as yet unchallenged, conclusions of a causal relation between reduced Ch4 cell number and memory loss [37]. These results cast doubt on the notion that alcoholic Korsakoff’s psychosis is a “basal forebrain” amnesia [39]. Although Ch4 cell loss cannot account for the amnesia of Korsakoff’s psychosis, lower Ch4 cell number may contribute to cognitive dysfunction in patients with Wernicke’s encephalopathy, both with and without Korsakoff’s psychosis [33,40].

Biochemical Aspects

Thiamine is a water soluble heat labile quaternary ammonia compound, containing an aminopyrimidine ring linked by a methylene bridge to a thiazole ring [41]. It is synthesized by different biochemical reactions in fungi, bacteria, plants and some protozoa, but not in humans [42].
In the human body it is found as unphosphorilated thiamine (i.e. free TH) and as phosphorilated derivates: thiamine monophospate (THMP), thiamine diphospate (THDP, aka TH pyrophosphate), and thiamine triphospate (THTP). Intracellularly, free thiamine is converted by thiaminyrophosphokinase into THDP, in a process requiring Magnesium as cofactor. Three plasma membrane bidirectional transporters for thiamine and thiamine derivates have been described: TH transporter 1 (THTR1) encoded by the SCL19A2 gene (location 1q23.3), TH transporter 2 (THTR2) encoded by the SCL19A3 gene (location 2q37) and reduced folate carrier transporter 1 (RFC1) encoded by the SCL19A1 gene (location 21q22.3). A mitochondria membrane transporter for THDP (i.e. mitochondria membrane THDP transporter) encoded by the SCL25A19 has also been described. THTR1 and THTR2 transport free TH. THTR1 seems to be highly expressed in skeletal and heart muscle and to lesser degrees in placenta, liver, kidneys, small intestine and lungs. THTR2 seems to be highly express in the placenta, kidneys, liver and thalamus and also in the small intestine. RFC1 is mainly a folate transporter, but also transports THDP and THMP. Considering that THDP is found exclusively intracellularly, RFC1 transports THDP only from the intracellular to the extracellular space (where THDP is rapidly converted to free TH). In the presence of low free TH and THMP plasma levels the cells that highly express RFC1 on their membranes have an overall negative TH balance, export-
ing THDP without importing free TH or THMP. RFC1 is highly expressed on the apical brush border of the choro-roid plexus. The intestinal absorption of thiamine occurs mainly in the proximal small intestine by an active stor-
able mechanism and probably also by passive diffusion.

At the intestinal brush border thiamine is mainly found in its free form. thiamine absorption is enhanced by thiamine deficiency and reduced by thyroid hormones, ethanol exposure, low temperature and thiamine analogues. Thiamine absorption may also be reduced in those with diabetes mellitus or advanced aged. At low concentration (<2 microM/liter) thiamine absorption is an active, rate-limited process, involving the high affinity THTR2 and, to a lesser extent, THTR1. At high intestinal thiamine concentration (5-50 microM/liter) thiamine seems to be absorbed through passive diffusion.

Thiamine has restricted distribution. Up to 90% of the circulating thiamine is found in the red cells (mostly as THDP), the rest being found in the other blood cells and in plasma, mainly bound by proteins, as free TH or THMP [43,44].

Under physiologic circumstances, thiamine is excret-
ed through kidney.

The blood brain barrier (BBB) allows the passage of free thiamine and THMP through both active and pas-
sive mechanisms. Active passage occurs at low thiamine serum concentrations. At high serum concentrations, free
Thiamine passes the BBB passively, driven by the existing concentration gradient.

Thiamine may have a structural role as part of the cellular membranes, and may be involved in the synaptic transmission, cellular differentiation, axonal growth, myelination and regulation of brain development during foetal and early postnatal life. To the best of our knowledge THMP and THTP have no clearly identified metabolic or structural roles [45]. THDP serves as a cofactor for several apoenzymes involved in the carbohydrate metabolism: apo-alpha-ketoglutarate dehydrogenase (aKGDH), apo-pyruvate dehydrogenase (PDH) and apo-transketolase (TK). Mg is the second cofactor required by these apoenzymes, especially by apo-TK. aKGDH and PDH are mitochondrial enzymes important for the tricarboxylic acid cycle (TAC, i.e. Krebs cycle), though the latter is not part of it. TK is a cytosolic enzyme involved in the nonoxidative phase of the pentose-phosphate pathway (PPP or hexose monophosphat shunt) [43].

It has been shown that TH deficiency inhibits the expression of the genes encoding TK and PDH [46,47]. Under physiologic circumstances, almost 30% of the brain glucose is metabolized to pyruvate. In the absence of a functional PDH complex and Krebs cycle pyruvate is reduced to lactate [48].

The human body has thiamine deposits ranging from 25 to 50 mg, commonly corresponding to the amount of thiamine required for 18 to 42 days. Most of the thiamine is stored in the liver as THDP. Food sources of thiamine are cereals, beans, nuts, brown (unpolished) rice and meat. Polished (white) rice, highly purified cereals and excessively cooked food may contain no thiamine. The daily thiamine requirements for a healthy adult may range from 1 to 2 mg and depend on the carbohydrate intake and on several metabolic factors. According to the current literature, the thiamine intake should be of at least 0.33 mg per 1000 kcal, ideally 0.5 mg per 1000 kcal, but no less than 1 mg per day.

Thiamine deficiency is the predisposing factor most frequently associated with Wernicke Encephalopathy.

Thiamine deficiency is the consequence of one or more of the following mechanisms: inadequate dietary intake (absolute or relative), impaired intestinal absorption, impaired storage, excessive elimination and/or increased metabolic requirements. Impaired thiamine intestinal absorption may occur due to gastrointestinal diseases, protein-caloric malnutrition (decrease in the active TH absorption) and/or ingestion of certain substances (e.g. ‘anti-TH factors’, antacids, phenytoin, cephalosporins, tetracycline). Impaired thiamine storage may occur also in chronic liver disease. Moreover, excessive renal elimination may occur due to renal disease, use of certain drugs and/or impaired thiamine storage. In those already marginally deficient Wernicke Encephalopathy may be precipitated by an event that rapidly increases the metabolic requirements of thiamine [19]. In most of the cases,
thiamine deficiency may be traced back to improper diet. Regardless of the cause, unbalanced nutrition persisting for more than 14 to 21 days, or even less in those already marginally deficient or with higher demands, may lead to thiamine deficiency. In healthy adults, intakes of less than 0.2 mg per 1000 kcal or of less than 0.66 mg per day lasting for several weeks lead to clinically manifest thiamine deficiency.

Gender may influence the risk of developing Wernicke Encephalopathy, possibly because of genetic differences but also because of gender-related environmental factors. No definite race predisposition has been described, but a population-specific susceptibility has been reported: it seems that Asians with thiamine deficiency are prone to cardiovascular beriberi, while Europeans with thiamine deficiency are more likely develop neurological beriberi and/or Wernicke Encephalopathy [2].

Chronic ethanol abuse is the condition most frequently associated to Wernicke Encephalopathy. Alcoholics may have higher thiamine demands, thiamine being necessary for the metabolism of ethanol. They frequently have thiamine intake below 0.29 mg per 1000 kcal and associate Mg depletion [5]. They may have impaired thiamine absorption secondary to ethanol-induced intestinal mucosa damage, impaired transmembrane transport due to folate or other B vitamins deficiency, decreased intestinal ATP-ase activity and reduced expression of the THTR1 and THTR2 encoding genes [49,50].

In the late 1970s, a biochemical study showed that, in fibroblasts from patients with Wernicke-Korsakoff syndrome (WKS), transketolase had decreased affinity for thiamine pyrophosphate [51]. The abnormality persisted through several generations of culture medium in the presence of excess thiamine and absence of ethanol. Thus, the occurrence of this enzyme variant may put individuals at risk for Wernicke’s encephalopathy when on a diet marginal or deficient in thiamine. This finding is consistent with other studies in isolated populations and in monozygotic twins concordant for WKS.

Although there were some variants in the nucleotide sequence of the transketolase coding region in fibroblasts derived from patients with WKS, there were no aminoacid sequence variations [43] or RNA splicing variants. Other mechanisms, such as post-translational modifications or different assembly of proteins, have been postulated to explain the difference in biochemical activity of transketolase in WKS. Furthermore, variation in the X-linked transketolase-like 1 (TKTL1) gene might also contribute to genetic susceptibility to WKS [52]. Other findings provide evidence for a role of the GABA-A receptor subunit gene cluster on chromosome 5q33 in susceptibility both to the alcohol-dependence syndrome and Korsakoff’s syndrome [53]. More recently, another gene coding for the high-affinity thiamine transporter protein SLC19A2 has been implicated in the pathophysiology of WKS [54,55].

Mutation screening identified three new genetic variants in the 3’ untranslated region of the high-affinity thia-
mine transporter in 25 people with alcoholism and WKS [55]. The 3L untranslated region is important in terms of gene regulation and protein expression [56]. Subtle genetic changes in the effectiveness of the various transport systems of thiamine in patients who develop Wernicke’s encephalopathy might ultimately lead to diminished ability to transport thiamine into brain cells. This functional impairment could contribute to an individual’s ability to cope with thiamine deficiency or respond to therapy [57].

Moreover, some gene polymorphisms, although not directly involved in the pathogenesis of WKS, might have a modifying role in the severity of clinical phenotype. One of the best characterised is the APOE ε4 allele, a well-known risk factor for Alzheimer’s disease. In patients with WKS and global intellectual deficiency, the frequency of the ε4 allele is significantly higher than in patients with WKS and preserved intellectual function other than amnesia, suggesting the involvement of this allele in the intellectual decline of patients [58].

In WKS several genetic defects might combine with environmental factors to generate the phenotype, and these genetic defects become clinically important when the diet is deficient in thiamine.

Thiamine deficiency leads to brain lesions—usually restricted to selective, vulnerable regions, with high thiamine content and turnover—within 2–3 weeks [59]. This timescale is related to the time necessary to deplete the body’s stores of thiamine, which are only sufficient for up to 18 days. After about 3 weeks of thiamine deficiency, the blood levels of thiamine also fall, leading to impaired function of enzymes requiring thiamine pyrophosphate as a coenzyme [59].

Thiamine in its metabolically active form, called thiamine pyrophosphate (TPP), is vital in the metabolism of carbohydrates. It serves a critical role in 3 enzyme systems: conversion of pyruvate to acetyl coenzyme A by pyruvate dehydrogenase, conversion of alpha-ketoglutarate to succinate by alpha-ketoglutarate dehydrogenase in the Krebs cycle catalysis by transketolase in the pentose monophosphate shunt [20].

In the presence of thiamine deficiency, these cellular systems dependent on thiamine begin to fail, leading eventually to cell death. Diminished transketolase activity results in failure of the maintenance of the myelin sheaths in the nervous system, metabolism of lipids and glucose, and production of branched chain amino acids. Lack of alpha-ketoglutarate dehydrogenase activity in the Krebs cycle alters cerebral energy utilization. If cells with high metabolic requirements have inadequate stores of thiamine to draw from, energy production drops, and neuronal damage ensues. Increased cell death feeds the localized vasogenic response. The alpha-ketoglutarate dehydrogenase complex (KGDHC) activity is considerably decreased in several brain regions that ultimately develop histological damage in Wernicke Encephalopathy [14,15,60] including the
Encephalopathy

thalamus. The earliest biochemical change is the decrease in α-ketoglutarate-dehydrogenase activity in astrocytes, which occurs after about 4 days of thiamine deficiency [60]. This is consistent with findings from animals with experimental thiamine deficiency, which consistently show early damage to glial cells rather than neurons [25,61] and patients with WKS, who have changes in astroglia together with microglial proliferation apparent even in regions of the brain with little if any neuronal cell death. A reduction in the activity of transketolase is noticed after about 1 week of thiamine deficiency, whereas no change in the activity of pyruvate dehydrogenase is observed for up to 10 days [60]. This metabolic impairment produces a diffuse decrease in the use of glucose in the brain, with consequent severe impairment of cellular energy metabolism [62]. In particular, many astrocyte related functions are impaired, such as the control of intracellular and extracellular glutamate concentrations (with probable occurrence of glutamate-mediated excitotoxicity), the maintenance of ionic gradients across the cell membrane, and blood–brain barrier permeability [20]. Moreover, in Wernicke’s encephalopathy at the symptomatic stage, increased lactate production by both neurons and astrocytes has been noticed, with intracellular accumulation of lactate, reductions in pH, and focal acidosis [63]. DNA fragmentation in thalamic neurons resulting in apoptotic cell death appears after about 2 weeks of thiamine deficiency [64].

Other mechanisms involved include mitochondrial dysfunction and intracellular oxidative stress with production of free radicals and cytokines as a result of early endothelial-cell dysfunction and increased production of nitric oxide [65]. The main consequence of these metabolic changes is the loss of osmotic gradients across cell membranes, with cytotoxic oedema and a progressive cell-volume increase firstly in astrocytes, then in neurons [66]. Decreased α-ketoglutarate-dehydrogenase activity resulting from thiamine deficiency, changes in the synthesis of amino acids, and the accumulation of lactate in the brain are initially reversible after prompt and sufficient thiamine therapy the so called stage of “reversible biochemical lesion” [66]. Conversely, a lack or delay of thiamine rehabilitation may lead to structural, irreversible lesions in selective regions of the brain with possible permanent neurological sequelae or a fatal outcome [19].

The loss of KGDHC activity is associated with reversible decreases in concentrations of the neuroactive amino acids glutamate, aspartate, and GABA, suggesting that these amino acids play a significant role in the development of this biochemical lesion. However, recovery of KGDHC activity and levels of GABA and aspartate following thiamine replenishment are incomplete, which may be indicative of permanent structural damage in this region. Additionally, the reduced production of succinate, which plays a role in GABA metabolism and the electrical stimulation of neurons, leads to further CNS injury. Increased lactic acid production ensues in the absence of
pyruvate dehydrogenase function, as the reduced conversion of pyruvate to acetyl coenzyme A results in less efficient oxidative phosphorylation.

Furthermore, the time course of onset of neurological symptoms of thiamine deficiency has been correlated with the fall in brain transketolase activity [67,68]. This enzyme is involved in the pentose phosphate shunt, an important pathway that supplies both ribose sugar residues necessary for nucleic acid synthesis as well as fatty acids for maintenance of membrane phospholipid integrity. In a recent study, it was revealed that decreased stability of the transketolase protein or a reduction in mRNA translation of the enzyme due to thiamine deficiency is the major factor responsible for the lowered activity [69]. Various studies provide evidence for an involvement of glutamate as an underlying mediator of CNS dysfunction and damage in PTD. Brain glutamate levels are reduced in whole brain of PTD animals as well as in vulnerable regions such as the pons and thalamus [14]. These findings are consistent with earlier reports of a decrease in the conversion of [14C] glucose to glutamate in symptomatic PTD rats [70,71] and reduced Ca2+ dependent release of glutamate in hippocampal slices from symptomatic animals [20]. Armstrong-James and co-workers [72] reported a similarity in the appearance and development of the central thalamic lesion in thiamine deficiency to that observed following intrathalamic administration of excitatory amino acids. Additionally, the extent of cell death can be reduced in brain regions affected in thiamine deficiency following treatment with the non-competitive NMDA receptor antagonist MK-801 [73,74]. Also consistent with glutamate excitotoxic mechanisms are the findings that extracellular glutamate concentrations are increased in the posterior thalamus during induction of Wernicke's encephalopathy [75]. It has been reported that the thalamus undergoes a process of apoptotic cell death in PTD rats [64]. Furthermore, a study of immediate-early genes (IEGs) revealed for the first time that the expression of c-fos, c-jun, fos-B and NGFI-A is dramatically increased in, and localized to, vulnerable regions of the brain such as the medial thalamus and inferior colliculi at the symptomatic stage of PTD in advance of the appearance of necrotic lesions [20]. An earlier increase in c-fos expression was also described in the same report, consistent with the initiation of a presymptomatic apoptotic event. IEGs encode transcriptional regulating factors that are induced following depolarization [76], a process also observed during PTD [20], and these factors are implicated in the control of genes which mediate both apoptosis and excitotoxic-induced cell death [77].

**Diagnosis**

Wernicke Encephalopathy is essentially a clinical diagnosis. The differential diagnosis should include several diseases like stroke and intracranial haemorrhage, meningitis and encephalitis, brain tumors, cerebellar diseases, toxic ingestions, liver failure, Marchiafava-Bignami disease, and metronidazole-induced encephalopathy.
Galvin et al in 2010 published a practical guidelines for diagnosis, management and prevention of the disease. Following their recommendation the clinical diagnosis of Wernicke Encephalopathy in alcoholics requires two of this four signs; dietary deficiencies, eye signs, cerebellar dysfunction, and either an altered mental state or mild memory impairment (Level B). The same recommendation might be applied also to non-alcoholic patients (GPP) [78].

Anyway other different biological tests and radiological examination may help in the diagnosis. Data from literature show that for the correct diagnosis the determination of thiamine blood concentration and red blood cell transketolase activity is recommended [79,67].

The erythrocyte transketolase activity assay including thiamine pyrophosphate effect has been replaced by direct measurement of thiamine and its phosphate esters in human blood by high-performance liquid chromatography (HPLC) [80,81]. Thiamine assay is available in many countries. Adult normal range (60–220 nM) and the lowest detectable level (3–35 nM) are given, however, normal thiamine levels do not necessarily exclude Wernicke Encephalopathy.

Radiological examinations and especially magnetic resonance are mandatory. The most frequently affected regions are the medial thalamus and periventricular region of the third ventricle (80%), followed by periaqueductal area (59%) and mammillary bodies (45%) [82,83].

Computed tomography (CT) can show areas of reduced attenuation density in the periaqueductal grey matter and in the medial portion of the thalami but, in most cases, can be totally negative in the acute phase of the disease [84].

MR might be more specificity and represent an important tool to get the right diagnosis [85]. Cytotoxic edema is usually shown on MR images, other typical findings may include alterations in the thalami, mammillary bodies, tectal plate, and periaqueductal area. Moreover in patients with Wernicke Encephalopathy due to alcoholism, other common finding include atrophy of the mammillary bodies, infratentorial regions, supratentorial cortex, and corpus callosum.

Usually in Wernicke Encephalopathy patients the cerebral alteration described on neuroimaging examination, are typically bilateral and symmetrical, with T2w and FLAIR (Fluid Attenuation Inversion Recovery) hyperintensities in the thalami, mammillary bodies, tectal plate, and periaqueductal area. Cerebellar signal intensity alterations can be observed in Wernicke Encephalopathy (both due to alcohol abuse or not), moreover autopsy studies have demonstrated that the anterior-superior vermis or anterior hemisphere is affected in more than half of patients with Wernicke Encephalopathy. The involvement of the caudate nuclei, in particular of the capita, may be due to their adjacent position to the lateral ventricles. Moreover, the presence of lesions of the caudate nuclei,
frequently observed in patients in comatose state, is a sign of pathologic evolution. Data from literature show that also cortical involvement brings to an irreversible damage and poor prognosis [86,87].

Sometimes TC and MRI scan may be negative, this however, does not exclude the diagnosis of Wernicke Encephalopathy. In alcoholic patients atrophy of the mammillary bodies and the cerebellar vermis are common (signs that are not found in non alcoholic ones) [88].

For the diagnoses of Wernicke Encephalopathy the contribution of CSF examination is still unclear. Very high CSF tau levels without increased p-tau have been found. It’s known that CSF tau has been proposed as a general marker for neuronal degeneration (CSF tau/p tau is increased in Alzheimer’s disease and other dementia syndromes), moreover the level of increase in CSF tau is highest in disorders with the most extensive neuronal degeneration, such as CJD (CSF tau levels and normal p-tau levels).

Autopsy series identifying typical brainstem lesions of Wernicke Encephalopathy have placed the incidence between 0.8% and 2.8% of the general population. However, the incidence can be as high as 12.5% in a population of alcoholics. It has been described in many other situations where nutrition has been compromised. These cases include patients with AIDS, individuals receiving hemodialysis, hyperemesis gravidarum, and malignancy with or without chemotherapy. Although it may not be diagnosed as frequently in third and fourth world nations, the incidence is probably higher in areas where there is more malnutrition and less vitamin supplementation. Studies suggest that up to 80% of patients with Wernicke encephalopathy may not be diagnosed, which makes estimates of mortality unreliable. Wernicke encephalopathy is a significantly disabling and potentially lethal condition that can be prevented or reversed if treated early. Established Wernicke encephalopathy can have major long-term consequences among patients requiring permanent institutional care. It is most often seen in alcoholics, but it can be seen in disorders associated with malnutrition and also in patients on long-term hemodialysis or with AIDS. The disease is frequently unrecognized and is likely more prevalent than commonly supposed [89,90].

**Treatment**

If Wernicke encephalopathy is suspected, prompt treatment with parenteral thiamine should be administered until there is no further improvement in signs and symptoms. Prophylactic thiamine supplementation should be considered in patients with alcoholism and malnutrition. Treatment include dietary supplements and thiamine [78]. Actually there is no consensus on the optimal dose of thiamine, according to literature data, treatment with either 100 or 200 mg thiamine given intravenously or intramuscular has been showed to be useful in non-alcoholics. This treatment has not always been curative in
alcoholics, probably because alcoholic patients with Wernicke encephalopathy may need higher doses and 500 mg three times daily has been recommended [2].

The administration of thiamine has been shown to be safe, and treatment should be started as soon as possible. Usually the unwanted side-effects to B vitamins are most commonly seen after multiple administrations, and mostly after intramuscular high dosage administration. It’s not clear if otherwise the supplementation of thiamine to food may prevent the development of Wernicke encephalopathy (GPP). The prophylactic parenteral administration of thiamine might be recommended only after bariatric surgery.

Therefore is still unclear the benefit of thiamine administration on cognitive impairment in Wernicke-Korsakoff syndrome. Noradrenaline, serotonin, glutamate and acetylcholine have been proposed in the pathogeny of the syndrome, but clear recommendation are still lacking. Other therapeutically non pharmacologically approach have been reported, new data show that the cognitive deficits relating to Korsakoff’s syndrome and non-amnesic alcoholism could be improved through cognitive rehabilitation [91,92]. Rehabilitation of memory has been mostly investigated. The use of elaborative processing, including extra processing time, explicit encouragement to generate associations and extra retrieval time to improve memory has been proposed in different trials. Elsewhere the use of self-generation and enactment of concepts to improve memory has been reported. Other data regard the improvement on executive functioning in Korsakoff’s syndrome.

**Conclusions**

Consideration for Wernicke encephalopathy should be given to patients with any evidence of long-term alcohol abuse or malnutrition and any of the following: acute confusion, decreased conscious level, ataxia, ophthalmoplegia, memory disturbance, hypothermia with hypotension, and delirium tremens. 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. Bariatric surgery, human immunodeficiency virus, hyperemesis gravidarum, and other disorders associated with grossly impaired nutritional status have been associated with Wernicke-Korsakoff syndrome. Additionally, infantile thiamine deficiency with manifestations of Wernicke syndrome has been reported in infants fed formula that was deficient in thiamine.

Implementation therapy, with thiamine is a fundamental approach for the treatment of WE: it must be avoided the administration of ev glucose, which may
cause a precipitation of thiamine defects. No therapy has been validated for the treatment of Korsakoff amnestic syndrome. Therefore, the clinicians should avoid any potential precipitating factor in specific patients, more at risk to develop Wernicke-Korsakoff syndrome.

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