ZEBRAS OF MEDICINE:
RECOGNISING WERNICKE ENCEPHALOPATHY AS THE UNDERLYING CAUSE OF A DELIRIUM

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Abstract

Wernicke encephalopathy (WE) is an acute neurological disease characterised by altered consciousness (drowsiness, delirium, coma), oculomotor symptoms, and gait ataxia caused by a thiamine deficiency. Thiamine deficiency is often caused by alcohol abuse, but it is also associated with other diseases, such as gastro-intestinal diseases. A timely diagnosis is of pivotal importance, as WE has a 20% mortality rate and, if left untreated, can lead to Korsakoff's syndrome [1, 2]. Korsakoff's syndrome is an irreversible chronic disease characterised by profound anterograde memory impairment, often accompanied by changes in behaviour [3]. Korsakoff's syndrome can be partially prevented by adequate diagnosis and treatment of WE. However, due to varieties in clinical presentation and the (relative) rarity of WE, it is often diagnosed late, especially in patients without a history of alcohol abuse [4]. One of the reasons WE can be misdiagnosed is that patients often present with confusion or altered mental status as the dominant symptom, *i.e.* the clinical syndrome of a delirium. Delirium is an acute neuropsychiatric disorder characterised by fluctuating changes in attention and mental status, often provoked by an underlying disease or infection in individuals already susceptible to experiencing delirium [5]. WE can be an underlying cause of a delirium and also present itself as such. In order to provide an overview of clues indicating WE to be the underlying cause of a delirium, this article delineates the pathophysiology, diagnostic process, and treatment of WE and delirium.

Pathophysiology

WE is caused by a thiamine (vitamin B1) deficiency due to a restrictive diet or decreased uptake [1]. Thiamine is present in almost all foods, including grain products, potatoes, meat, vegetables, and milk, which means that it is difficult to develop a thiamine deficiency if one maintains a balanced diet [1, 6]. Thiamine is absorbed in the gut by enterocytes, after which approximately 80% is converted into thiamine diphosphate (TPP), which forms our intracellular storage of thiamine [7]. On average, healthy people have a total of 30-50 mg thiamine stored intracellularly [1, 3]. With an average requirement of 1-2 mg of thiamine per day, the storage in the cells would provide 4-6 weeks' worth of thiamine in case of restrictive intake [1, 3]. This is in line with several studies that show that symptoms begin to emerge a few weeks after the start of a decreased intake of thiamine [1, 6]. TPP is involved in a wide range of functions within the cell, the most important of which is its function as a cofactor for several enzymes involved in the Krebs cycle. A lack of TPP will disrupt the Krebs Cycle, resulting in cell death through decreased ATP production, oxidative stress leading to DNA and RNA instability, and a build-up of toxic metabolites such as lactate [7]. As some thiamine-dependent enzymes also require magnesium as a cofactor, it is important to also determine magnesium levels to see if there is an additional deficiency [1]. Thiamine deficiency can cause two different diseases, namely, beriberi, presenting with peripheral neuropathy (dry beriberi) or cardiac failure (wet beriberi) and WE [8]. WE will be the primary focus of this article.

The patient group of WE mainly consists of patients suffering from alcohol dependence, with around 90% of patients with WE actively abusing alcohol in industrialised countries [1]. However, other diseases affecting intake or absorption of thiamine can also lead to WE. These include, for instance, bariatric surgery, malabsorption syndromes, or hyperemesis [9]. Interestingly, alcohol abuse itself, regardless of nutrition state, increases the chance of developing WE [1]. Patients suffering from alcohol abuse were reported to already have lower levels of serum thiamine. A deficiency in thiamine, in turn, decreases the uptake of thiamine by enterocytes, thereby additionally depriving the patients of thiamine [1]. Ethanol can further damage the intestinal epithelium, which can reduce thiamine absorption up to 90% [1]. Moreover, liver disease such as cirrhosis, often seen in alcoholics, impairs the conversion of thiamine into TPP and decreases the amount of thiamine stored in the cells [1, 3]. The first therapy for ascites, a known complication of liver cirrhosis, is the diuretic furosemide, which decreases the renal tubular reabsorption of thiamine [1]. All in all, patients who are alcohol abusers, especially after developing liver cirrhosis, have a higher chance of developing WE due to thiamine deficiency. However, although WE is more common in patients with active alcohol abuse, the absence of alcohol abuse does not rule out WE.

The pathophysiology for delirium caused by other causes is not entirely elucidated; the range of underlying conditions is sheer endless. The cellular mechanisms underlying the development of delirium remain largely unknown. The current theory surrounding the pathophysiology of delirium focuses on patient vulnerability, implying that patients associated with a large number of risk factors require fewer precipitants to develop delirium than individuals with a lower number of risk factors (Figure 1) [5, 10]. The main risk factors include old age, comorbidities, and neurocognitive deficits, with between 20-30% of elderly admitted with acute disease developing delirium [5, 10]. The precipitants can be a wide range of factors, varying in severity. Examples include infection, surgery, trauma, or other diseases [5, 10]. Correctly identifying and treating delirium is important, as delirium negatively affects health outcomes, including long-term symptoms, such as cognitive decline, and mortality [5].

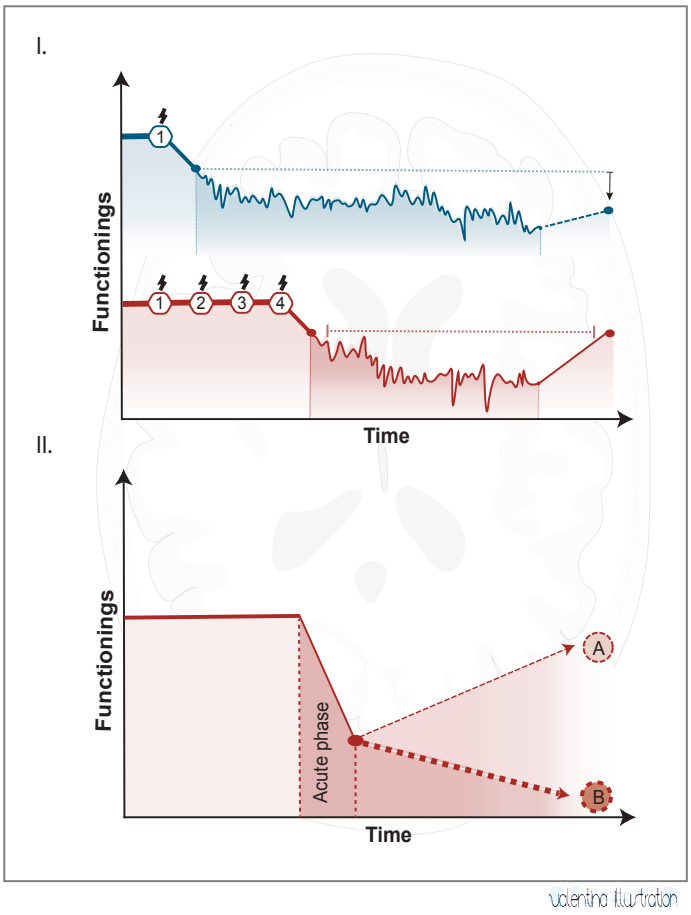

Figure 1: *Wernicke encephalopathy is characterised by an acute decrease in functioning, of which a part will recover fully. However, a significant amount of patients will have residual symptoms or continue to develop Korsakoff's syndrome. A delirium caused by other factors will require fewer precipitants in already susceptible individuals and is characterised by an acute decrease in functioning with a fluctuating course. Development of a delirium can also affect long-term health outcomes and functioning, especially in elderly.*

Clinical presentation

Carl Wernicke first described WE in 1881, when three patients presented with similar symptoms, namely ataxia, ophthalmoplegia, and changes in consciousness or mental confusion [4]. After this triad of symptoms had been described a few more times in literature, it was referred to as the classic triad. The acute stage of WE, characterised by symptoms from the classic triad, is preceded by a less acute phase with non-specific symptoms, such as gastro-intestinal irritation, fatigue, and irritability (Figure 1) [3]. These non-specific symptoms can emerge six to eight weeks after the start of the thiamine deficiency [1]. During the acute phase, all three symptoms of the classic triad are present in only 16-33% of patients [2-4]. The majority of patients present exclusively with mental changes, e.g. confusion, memory impairment, or problems concentrating [2]. Moreover, patients not suffering from alcohol abuse present less often with the classic triad, making the diagnostic process more difficult [2]. Other symptoms that can occur besides the classic triad are autonomic symptoms, seizures, vestibular dysfunction, and peripheral neuropathy. The European guidelines currently require the presence of two of the following symptoms in order to diagnose WE: I) ocular symptoms, II) cerebellar dysfunction, III) restricted intake, and IV) an altered mental state or mild memory impairment [11].

Patients with delirium due to other causes also present with an altered mental status: an acute and fluctuating decrease in attention, often accompanied by other symptoms. The diagnostic and statistical manual of mental disorders (DSM-V) requires the presence of the following symptoms in order to diagnose delirium: I) an acute onset (hours-days) of symptoms, II) disruption of attention, III) disruption of cognitive function, which can include changes in perceptions, e.g. hallucinations, IV) an underlying physical cause based upon physical examination or laboratory values, and V) no other neurocognitive explanation of the symptoms [12]. Nonetheless, the clinical presentation of delirium differs based on the type of delirium. Hyperactive delirium is often diagnosed more easily, as it is characterised by hyperactive psychomotor activity, which can lead to agitation [12]. Hypoactive delirium, on the other hand, is more often overlooked, as it is characterised by low psychomotor activity and sogginess [12]. However, patients can also present with the mixed subtype, where there is a normal level of psychomotor activity or rapidly fluctuating psychomotor activity [12]. WE should always be considered in the differential diagnosis of a delirium; however, patients with delirium caused by other factors generally do not exhibit the neurological symptoms from the classic triad [12].

Further testing

WE and delirium are both clinical diagnoses, which means that the diagnosis is primarily based upon the clinical presentation. In the case of WE, it is possible to determine thiamine levels, either by measuring serum thiamine levels or erythrocyte thiamine transketolase activity [13]. However, determination of thiamine levels is not to be awaited in clinical practice. Serum thiamine levels do not necessarily correspond to cerebral thiamine levels and are therefore not used to determine or exclude WE [14]; patients can have WE despite normal serum thiamine levels [14]. Furthermore, treatment should start immediately when the suspicion of WE arises, without awaiting thiamine levels, in order to prevent irreversible damage, including Korsakoff's syndrome [13].

Although typical lesions indicating WE can be seen on neuroimaging, imaging is not used routinely to establish the diagnosis of WE either. Magnetic resonance imaging (MRI) can show lesions typical for WE, which include an increased T2-signal and decreased T1-signal periaqueductally, and within the mamillary bodies, medial thalamus, dorsal medulla, and tectal plates [2]. Atrophy of the mammillary bodies is a specific finding, as is not often seen with other disorders, but that can not be seen yet during the acute stage [15]. However, despite the high specificity of MRI, the sensitivity remains low, which means it can not be used to rule out WE [16]. Nonetheless, MRI can be used to rule out alternative diagnoses, such as rare focal neurological disorders mimicking the symptoms of WE.

Delirium is a clinical diagnosis, with the criteria provided by the DSM-V providing a clear framework [12]. The DSM-V criteria also require further testing in order to identify an underlying physical cause. Therefore, routine laboratory testing is always performed in case of a delirium in order to determine possible underlying causes, e.g. electrolyte disbalance or a urinary tract infection. Imaging is performed according to the patient's (or caregiver's) story and physical examination: if there are indications for neurological causes such as a stroke, a CT-cerebrum can be performed, whereas coughing and a fever are an indication for a chest X-ray. If the cause of the delirium remains unknown, meningitis could be the cause, which is an indication for a lumbar puncture [17].

Treatment and prognosis

WE is treated with supplementation of thiamine; however, there are discrepancies in terms of the recommended dosage of thiamine in different national guidelines. The EU guidelines suggest administration

of 200 mg intravenously three times a day, whereas the Dutch national guideline advises 500 mg intravenously three times a day [11, 18]. Different clinical trials have been carried out to determine the dosage of thiamine supplementation, but an exact dosage has not been identified hitherto. However, despite differences in the exact dosage of thiamine, the currently existing guidelines do agree that treatment should start immediately when the clinical suspicion of WE arises to prevent complications or death. Furthermore, oral supplementation of thiamine is not recommended, as damage to the gastro-intestinal mucosa by e.g. alcohol abuse causes a decreased uptake of thiamine, hindering its effect [11]. Thiamine must, therefore, always be given intravenously or intramuscularly in the acute phase. Thiamine should be administered before administering glucose as well, since a high glucose load may precipitate WE. After the acute phase, intravenous supplementation of thiamine can be substituted by oral supplementation [11, 18]. In addition, thiamine deficiency is often accompanied by other deficiencies, notably magnesium, sodium, and phosphate deficiencies [11, 18]. Levels there of should be measured at the start of treatment, and these minerals should also be supplemented as needed [11, 18]. Besides supplementation, a crucial component of the treatment of WE is to quit alcohol consumption and prevent relapse.

The prognosis of WE depends on the severity of the disease, time of treatment, and comorbidities of the patient. The symptoms tend to improve in a typical fashion after supplementation of thiamine. The ocular abnormalities will usually improve within hours or days; if the ocular symptoms do not improve after thiamine supplementation, the diagnosis of WE should be reconsidered [19]. The gait ataxia tends to improve, but the recovery is occasionally incomplete, leaving patients with residual symptoms [19]. The confusion will dampen over time, but usually requires weeks to months for a full recovery. Patients can have persistent mental deficits, of which only 20% of patients will recover partially or completely (Figure 1). The other patients will have permanent anterograde memory impairment and will develop Korsakoff's syndrome despite adequate treatment (Figure 1) [13]. It is important to note that thiamine can also be given as a precaution to patients at-risk, e.g. presenting with alcohol withdrawal, to prevent these long-term consequences.

Delirium will not subside until the underlying cause has been treated properly. Therefore, it is crucial to also diagnose and treat the precipitant of the episode [17]. This differs per patient, which means that a patient-specific treatment plan needs to be made – e.g. antibiotics to treat infection or supplementation of electrolytes in case of an electrolyte imbalance [17]. In the meantime, the delirium can be treated symptomatically, using either non-pharmacological or pharmacological interventions. It is advised to start with nonpharmacological interventions: providing a calm and safe environment and reassurance from the staff or family present [17, 20]. If this does not provide enough relief, and the patient remains agitated, scared, or restless, pharmacological treatment can be considered. Antipsychotics, haloperidol specifically, are considered to be the first pharmacological treatment option, but the most suitable medication differs depending on the comorbidities of the patients [17]. In case of (relative) contraindications, newer antipsychotic drugs, often referred to as atypical antipsychotic drugs, can be prescribed. These may or may not be combined with benzodiazepines. However, one must bear in mind that medications such as antipsychotics can also have side effects, including increased risk of cardiovascular events and an increased risk of falls – which can have severe consequences in the elderly [17]. It is therefore advised to prescribe psychotropic medication with caution. There is no psychopharmacological treatment for a hypoactive delirium, as the medication is aimed at reducing agitation or restlessness, which is not present in the case of a hypoactive delirium [20]. Delirium is associated with increased mortality [21]. Furthermore, a recent meta-analysis by Goldberg *et al.* showed that patients with delirium experienced cognitive decline three months after the episode, suggesting that patients can experience chronic long-term cognitive effects of a delirium [22].

Conclusion

To conclude, the predominant clinical symptom of WE can be a delirium, with confusion and altered mental status as the dominant symptom. In case of WE, patients may also exhibit other symptoms, such as ophthalmoplegia and gait ataxia, whereas patients with delirium caused by other precipitants will show fluctuations throughout time as well as symptoms from an underlying precipitant of the delirium. Hence, it is important to perform a thorough physical examination and history – both with the patient and their caregiver - to determine any symptoms indicating WE as the underlying cause of the delirium or other possible precipitants for a delirium. Correctly identifying WE as the underlying cause of the delirium is crucial, as untreated WE leads to Korsakoff's syndrome, causing permanent cognitive deficits, and an unrecognised and undertreated delirium also affects health outcomes negatively, including mortality and long term cognitive decline. WE should, therefore, always be included in the differential diagnosis of a delirium.

Acknowledgement

RAMS would like to thank Prof. Dr. Edo Richard, from the department of neurology at Radboud University Medical Center, and Daphne Olischläger, BSc., for providing the author of this article with feedback.

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CORRECT ANSWERS TO THE EXAM QUESTIONS

Answer question 1:
B. 5-hydroxytryptamine

The majority of the tricyclic antidepressants act primarily as serotonin (5-hydroxytryptamine) and norepinephrine reuptake inhibitors by blocking both the serotonin and norepinephrine transporter, which results in an elevation of the synaptic concentrations of these neurotransmitters. This enhances neurotransmission. However, they have a weak affinity for the dopamine transporter and, therefore, low efficacy as dopamine reuptake inhibitors. Tricyclic antidepressants block the muscarinic acetylcholine receptors.

For further reading:
Siegel, A., Sapru, H. Chapter 7: Neurotransmitters in Essential Neuroscience, 4th edition (Wolters Kluwer, Philadelphia, 2019).

Answer question 2:
C. Both donor tolerogenic cells and regulatory T cells

Tolerogenic dendritic cells are heterogenous pools of dendritic cells with immunosuppressive properties, priming the immune system into a tolerogenic state against various antigens. These cells induce immune tolerance by inhibiting the activation of T cells and inducing regulatory T cell proliferation. Regulatory T cells are a specialised subpopulation of T cells that act to suppress immune response, thereby maintaining homeostasis and self-tolerance. It has been shown that they are able to inhibit T cell proliferation and cytokine production. These mechanisms help preventing rejection by antigen specific tolerance.

For further reading:
Li, H., & Shi, B. (2015). Tolerogenic dendritic cells and their applications in transplantation. *Cellular & molecular immunology*, 12(1), 24–30.
Oberholtzer, N., Atkinson, C., & Nadig, S. N. (2021). Adoptive Transfer of Regulatory Immune Cells in Organ Transplantation. *Frontiers in Immunology*, 12.

The exam questions can be found back on page 12 in this journal.