CASO CLÍNICO/CASE REPORT

Non-Alcohol-Related Wernicke Encephalopathy

Encefalopatia de Wernicke Não Relacionada com Consumo de Álcool

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Abstract

A 39-year-old male with a recent diagnosis of human immunodeficiency virus infection, in the AIDS stage, and Burkitt lymphoma, both identified in the context of a constitutional syndrome with six months of evolution developed an acute condition with psychomotor slowing, disorientation, and gait imbalance, six weeks after initiating antiretroviral therapy and chemotherapy. Neurological examination revealed multidirectional nystagmus, length-dependent sensory disturbance, and severe appendicular and gait ataxia. Brain MRI showed symmetrical hyperintensity in the medial thalami, extending to the posterior midbrain, pons, and medulla. With a clinical suspicion of Wernicke's encephalopathy, high-dose intravenous thiamine supplementation was initiated, resulting in rapid clinical improvement and imaging regression of the lesions.

This case highlights an atypical and potentially reversible presentation of Wernicke's encephalopathy, underscoring the importance of clinical suspicion in patients with severe cachexia, hematologic malignancies, or other conditions that impair thiamine absorption.

Resumo

Homem, 39 anos, com diagnóstico recente de infeção por vírus da imunodeficiência humana, estadio de SIDA, e linfoma de Burkitt, identificados no contexto de síndrome constitucional com seis meses de evolução. Seis semanas após o início de terapêutica antirretrovírica e quimioterapia, desenvolveu um quadro agudo de lentificação psicomotora, desorientação e desequilíbrio da marcha. O exame neurológico revelou nistagmo multidirecional, alteração da sensibilidade de tipo distância-dependente e ataxia grave apendicular e da marcha. A ressonância magnética cerebral mostrou hipersinal simétrico nos tálamos mediais, com extensão ao mesencéfalo posterior, ponte e bulbo. Perante suspeita de encefalopatia de Wernicke, cumpriu suplementação com tiamina endovenosa em alta dose, com rápida melhoria clínica e regressão imagiológica das lesões.

Este caso destaca uma apresentação atípica e potencialmente reversível da encefalopatia de Wernicke, sublinhando a importância da suspeita clínica em doentes com caquexia grave, neoplasias hematológicas ou outras condições que comprometam a absorção de tiamina.

Introduction

Wernicke encephalopathy (WE) is a neurological disorder induced by thiamine deficiency, characteristically associated with chronic alcoholism. We report a patient with an infrequent cause of thiamine deficiency: severe consumption status in advanced human immunodeficiency virus (HIV) infection and lymphoproliferative disease.

Case Report

A 39-year-old man with a history of high-risk sexual behaviour and previously treated primary syphilis, with no history of alcohol consumption, presented to the emergency department of a tertiary hospital with a constitutional syndrome: involuntary weight loss of 20 kg over six months, anorexia, asthenia, frequent vomiting, and persistent fever lasting at least 72 hours, associated with bilateral cervical adenopathies with progressive growth over two months. Laboratory tests revealed severe pancytopenia (hemoglobin 6.5 g/dL, platelet count 13 × 10^9/L, and leukocyte count 5300/μL), requiring transfusional support. Physical examination showed extensive lymphadenopathy (cervical, mediastinal, retroperitoneal, and inguinal) as well as hepatosplenomegaly.

Upon admission, the patient also reported achromatopsia; however, there were no changes in visual acuity or color vision and no relative afferent pupillary defect in the ophthalmological evaluation. Fundoscopic examination demonstrated bilateral pre-retinal hemorrhages and cotton-wool spots adjacent to the vascular arcades, without evidence of papilledema, vitritis, optic disc edema, or leakage on fluorescein staining. Following the study, the diagnosis of HIV infection was established, classified as stage C3 according to the Centers for Disease Control and Prevention (CDC) criteria, with a nadir CD4+ T-cell count of 37 cells/mm³ and a plasma HIV-RNA load of 4 410 000 copies/mL. Simultaneously, the patient was diagnosed with stage IV Burkitt lymphoma (Ann Arbor classification).

Due to the clinical severity and aggressive nature of the lymphoproliferative disease, antiretroviral therapy (ART) with emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) and dolutegravir (DTG) was initiated immediately. Chemotherapy was commenced according to the Burkimab protocol, and prophylactic treatment with trimethoprim/sulfamethoxazole and valganciclovir was introduced. Six weeks later, the patient revealed behavioral changes, marked by psychomotor slowing, temporal-spatial disorientation and gait imbalance. Neurological examination revealed reduced attention span with difficulty in both capturing and sustaining attention, multidirectional nystagmus, and mild tetraparesis—graded 4+/5 in the upper limbs and 4/5 in the lower limbs according to the Medical Research Council scale. There was marked generalized muscle atrophy (in a patient with a cachectic state), but no fasciculations, with a global hyporeflexia and flexor plantar responses. Sensory examination revealed a length-dependent gradient of impairment, and there was severe appendicular and truncal ataxia. Gait was broad-based and markedly unstable. Laboratory investigations excluded active infections by herpes group viruses and *Toxoplasma gondii*, as well as deficiencies in folic acid (3.2 ng/mL) and vitamin B12 (302 ng/L). Blood cultures showed no microbial growth. Vitamin B1 levels were not measured, as the assay was unavailable at our center. Lumbar puncture revealed a normal opening pressure (16 cmH_2O) and mild protein elevation (0.74 g/dL), without pleocytosis (3 cells/μL) or hypoglycorrhachia. Microbiological analysis of the cerebrospinal fluid was negative for viral, bacterial, and fungal pathogens, including bacteriological, serological, and mycological testing and HIV RNA was not detected in the cerebrospinal fluid. Specific serologic tests (treponemal and non-treponemal, Wright reaction, and cryptococcal antigen) were also negative and polymerase chain reaction (PCR) testing did not detect DNA from herpes group viruses, hepatitis E virus, JC virus, *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Nocardia* spp., *Aspergillus fumigatus*, or *Toxoplasma gondii*. Cerebrospinal fluid immunophenotyping showed no evidence of lymphomatous cells. Electrophysiological studies revealed reduced conduction velocities and low-amplitude motor and sensory potentials in both the upper and lower limbs, which were consistent with sensorimotor polyneuropathy.

Brain magnetic resonance imaging (MRI) depicted symmetric, bilateral hyperintensities in the medial thalamus, extending to the posterior mesencephalon, pons, and medulla (**Fig. 1**).

The diagnosis of Wernicke's encephalopathy was established based on clinical and imaging findings and treatment was initiated with high-dose intravenous thiamine (500 mg three times daily for one week, followed by 300 mg twice daily for an additional week, and sub-

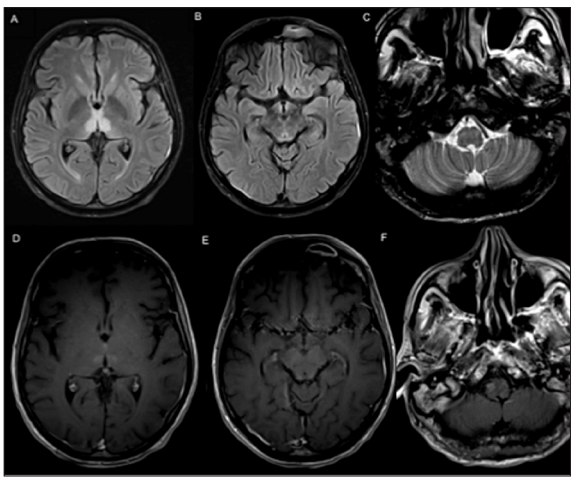

Figure 1. Brain MRI before treatment. (A) (B) Axial 2D T2W FLAIR revealing bilateral hyperintensity of the medial thalamus, extending to the hypothalamus, inferior colliculus and periaqueductal grey matter. (C) Axial 2D T2 TSE showing bilateral pyramidal hyperintensity in the medulla oblongata. (D) (E) and (F) Axial 2D T1 SE revealing tenuous enhancement of the previously mentioned affected areas.

sequently transitioned to oral thiamine 100 mg daily), along with parenteral supplementation of cobalamin and folic acid, resulting in prompt clinical improvement. Follow-up MRI on day 15 demonstrated marked regression of the previously observed lesions (**Fig. 2**).

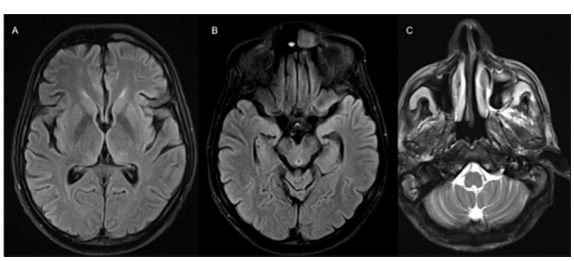

Figure 2. Brain MRI after treatment. (A) (B) Axial 2D T2W FLAIR and (C) axial 2D T2 TSE showing almost complete resolution of the hyperintense areas 2 weeks after treatment.

Discussion

This case illustrates symptomatic thiamine deficiency in the setting of severe wasting secondary to newly diagnose acquired immunodeficiency syndrome (AIDS) and lymphoproliferative disease.[1] Although WE is classically associated with chronic alcohol use, this report highlights the need to consider less common, non-alcohol-related aetiologies.[2]

WE is a neurological syndrome resulting from thiamine (vitamin B1) deficiency, a vital coenzyme in multiple metabolic pathways within the central nervous system. In both neurons and glial cells, thiamine facilitates ATP production, lipid metabolism, and the synthesis and maintenance of the myelin sheath. It also plays a crucial role in the synthesis of glucose-derived neurotransmitters, such as glutamate and gamma-aminobutyric acid (GABA), and contributes to cholinergic and serotonergic neurotransmission, as well as axonal conduction. Deficiency of thiamine leads to impaired cerebral energy metabolism, culminating in neuronal dysfunction, brain lesions, and eventual cell death.[3]

While WE is commonly associated with chronic alcohol use, non-alcoholic causes are increasingly recognized as potential triggers for both acute and chronic presentations of the syndrome, particularly in malnourished or immunocompromised patients, characterized by heightened metabolic demand or impaired thiamine absorption. The classic triad of altered mental status, gait ataxia, and oculomotor dysfunction is present in only one-third of cases. Additional features, such as blurred vision, papilledema, seizures, hearing loss, hallucinations, hyporeflexia, distal paraesthesias, and gastrointestinal symptoms, may also occur. Importantly, altered mental status alone may be the only presenting feature and should raise suspicion for WE in at-risk populations.[4,5]

Hematological malignancies, including Burkitt lymphoma, represent important non-alcoholic risk factors, as they are frequently associated with accelerated cellular turnover, malnutrition, and gastrointestinal dysfunction, factors often exacerbated by intensive chemotherapy regimens.[5-7] In oncological settings, a high index of clinical suspicion remains the cornerstone for timely diagnosis of WE.

Immunocompromised individuals, particularly those living with HIV, are predisposed to thiamine deficiency due to a combination of factors, including increased metabolic requirements, gastrointestinal malabsorption, cachexia, systemic inflammation, and a sustained hypercatabolic state.[8] In a study by Butterworth *et al*, thiamine deficiency was identified in 9 of 39 patients with AIDS, highlighting its clinical relevance in this population.[9]

In the present case, the patient had a recent diagnosis of AIDS (CDC stage C3, $CD4^+$ count 37 cells/mm^3) and stage IV Burkitt lymphoma, both conditions associated with marked catabolic stress and profound nutritional compromise, likely contributing to thiamine depletion. Furthermore, he was receiving combined antiretroviral therapy (ART), systemic chemotherapy, and prophylactic treatment with valganciclovir and sulfamethoxazole/

trimethoprim. Several of these agents, notably high-dose methotrexate, cytarabine, and certain protease inhibitors, have established neurotoxic potential, which may further exacerbate underlying metabolic vulnerability or independently contribute to peripheral and central neurotoxicity.[10]

Although WE remains fundamentally a clinical diagnosis, supportive investigations, including biochemical assays and neuroimaging, may aid in confirmation and should be considered when clinical suspicion arises.

No single laboratory test definitively confirms vitamin B1 deficiency. Nonetheless, functional assays, such as erythrocyte transketolase activity with thiamine pyrophosphate stimulation, may provide useful information, although these are not widely available. Serum or whole blood thiamine levels, including thiamine pyrophosphate, can be measured chromatographically; however, their sensitivity and specificity in symptomatic individuals remain uncertain.[11,12]

Neuroimaging, while not required for diagnosis, may support clinical suspicion and help exclude alternative etiologies. In non-alcoholic WE, brain MRI typically reveals symmetric T2/FLAIR hyperintensities in the medial thalami, mammillary bodies, periaqueductal grey matter, tectal plate, third ventricle, cranial nerve nuclei, and regions anterior to the fourth ventricle. MRI findings may also hold prognostic value, as cortical involvement can suggest irreversible damage, although some cases, such as those described by Doss and D'Aprile, indicate the potential for recovery despite such changes. Mammillary body atrophy remains a characteristic feature of chronic WE.[13-17] Notably, MRI supported the diagnosis in more than 66% of non-alcoholic cases reviewed by Oudman,[9] though sensitivity varies according to the underlying condition.

In the present case, neurological symptoms developed approximately six weeks after introducing antineoplastic and antiretroviral therapy. MRI demonstrated symmetric T2/FLAIR hyperintensities involving the medial thalami, mesencephalon, and pons, without evidence of opportunistic infection, neoplastic infiltration, or ring-enhancing lesions. No restricted diffusion or infarct patterns were noted. The mild, non-specific contrast enhancement observed is atypical for lymphoma. The symmetry and anatomical localization of lesions, alongside the absence of widespread parenchymal involvement, argued against an infectious cause, though this cannot be definitively excluded in immunocompromised patients and must be analyzed alongside clinical and laboratory findings.

Cerebrospinal fluid (CSF) analysis revealed normal opening pressure, absence of pleocytosis, mild protein elevation, and negative results for microbiological, mycobacterial, and fungal studies. These findings effectively excluded common central nervous system (CNS) opportunistic infections, acute bacterial or fungal meningitis, and CNS involvement by lymphoma.

Peripheral nerve conduction studies demonstrated reduced conduction velocities and low-amplitude motor and sensory responses, consistent with a sensorimotor polyneuropathy. This was interpreted as likely multifactorial, attributable to nutritional deficiencies, neurotoxic effects of chemotherapy, and potentially ART. Despite these findings, treatment regimens were continued, and parenteral vitamin supplementation was initiated, resulting in clinical improvement, although not complete.

Given the clinical context of severe malnutrition, hypercatabolic state, cachexia, and polypharmacy, a metabolic-toxic etiology was considered most likely. The combination of clinical features, characteristic neuroimaging findings, and the observed rapid improvement following high-dose intravenous thiamine administration supported the diagnosis of Wernicke encephalopathy (WE).

Timely recognition and prompt treatment with thiamine are essential to prevent irreversible neurological injury and to reverse acute manifestations. The European Federation of Neurological Societies and the Royal College recommend parenteral administration of 500 mg of thiamine three times daily until acute symptoms resolve.[18]

Conclusion

In patients with hematological malignancies or immunocompromised states, the acute or subacute onset of neurological symptoms, particularly when accompanied by atypical clinical features or signs suggestive of thiamine deficiency, should raise clinical suspicion for WE. Thiamine depletion may result from nutritional compromise, increased metabolic demand, or impaired cellular metabolism. Given its favorable safety profile, thiamine should be administered empirically when WE is suspected. Early recognition and prompt administration of high-dose parenteral thiamine are critical to reversing neurological dysfunction, preventing irreversible damage, and halting progression to Korsakoff's syndrome.

In this case, timely intervention led to rapid clinical improvement and prevented further complications. ■

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RNR, BB and CC: Research, conception, organization and elaboration of the manuscript.

CS and AC: Clinical evaluation of patient, drafting of the manuscript and revision of the manuscript.

All authors approved the final version to be published.

RNR, BB e CC: Pesquisa, conceção, organização e elaboração do manuscrito.

CS e AC: Avaliação clínica do doente, elaboração do manuscrito, revisão do manuscrito.

Todos os autores aprovam a versão final a ser publicada.

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References / Referências

1. Scalzo SJ, Bowden SC, Ambrose ML, Whelan G, Cook MJ. Wernicke-Korsakoff syndrome not related to alcohol use: a systematic review. J Neurol Neurosurg Psychiatry. 2015;86:1362-68. doi: 10.1136/jnnp-2014-309598.
2. Silvariño R, Duthil J, Zubiaurre V, Rebella M, Gutiérrez M, Sosa L. Encefalopatia de Wernicke secundaria a hiperemesis gravídica. Rev Neurol. 2008;47:274-75
3. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol. 2007;6:442–55. doi: 10.1016/S1474-4422(07)70104-7.
4. Thomson AD, Cook CC, Guerrini I, Sheedy D, Harper C, Marshall EJ. Wernicke's encephalopathy revisited. Translation of the case history section of the original manuscript by Carl Wernicke 'Lehrbuch der Gehirnkrankheiten fur Aerzte and Studirende' (1881) with a commentary. Alcohol Alcohol. 2008;43:174-9. doi: 10.1093/alcalc/agm144.
5. Ghishan FK, Kiela PR. Vitamins and Minerals in Inflammatory Bowel Disease. Gastroenterol Clin North Am. 2017;46:797-808. doi: 10.1016/j.gtc.2017.08.011.
6. Isenberg-Grzeda E, Rahane S, DeRosa AP, Ellis J, Nicolson SE. Wernicke-Korsakoff syndrome in patients with cancer: a systematic review. Lancet Oncol. 2016;17:e142-8. doi: 10.1016/S1470-2045(16)00037-1.
7. Oudman E, Wijnia JW, van Dam M, Biter LU, Postma A. Preventing Wernicke Encephalopathy After Bariatric Surgery. Obes Surg. 2018;28:2060-8. doi: 10.1007/s11695-018-3262-4.
8. Gui QP, Zhao WQ, Wang LN. Wernicke's encephalopathy in nonalcoholic patients: clinical and pathologic features of three cases and literature reviewed. Neuropathology. 2006;26:231–5.
9. Butterworth RF, Gaudreau C, Vincelette J, Bourgault AM, Lamothe F, Nutini AM. Thiamine deficiency and Wernicke's encephalopathy in AIDS. Metab Brain Dis. 1991;6:207-12. doi: 10.1007/BF00996920.
10. Ribera JM, García O, Grande C, Esteve J, Oriol A, Bergua J, et al. Dose-intensive chemotherapy including rituximab in Burkitt's leukemia or lymphoma regardless of human immunodeficiency virus infection status: final results of a phase 2 study (Burkimab). Cancer. 2013;119:1660-8. doi: 10.1002/cncr.27918.
11. Leigh D, McBurney A, McIlwain H. Erythrocyte transketolase activity in the Wernicke-Korsakoff syndrome. Br J Psychiatry. 1981;139:153–6.
12. Harper CG, Giles M, Finlay-Jones R. Clinical signs in the Wernicke- Korsakoff complex: a retrospective analysis of 131 cases diagnosed at necropsy. J Neurol Neurosurg Psychiatry. 1986;49:341–5.
13. Fei GQ, Zhong C, Jin L, Wang J, Zhang Y, Zheng X, et al. Clinical characteristics and MR imaging features of nonalcoholic Wernicke encephalopathy. AJNR Am J Neuroradiol. 2008;29:164-9. doi: 10.3174/ajnr.A0827.
14. Oudman E, Wijnia JW, Oey MJ, van Dam M, Postma A. Wernicke-Korsakoff syndrome despite no alcohol abuse: A summary of systematic reports. J Neurol Sci. 2021 426:117482.
15. D'Aprile P, Tarantino A, Santoro N, Carella A. Wernicke's encephalopathy induced by total parenteral nutrition in patient with acute leukaemia: unusual involvement of caudate nuclei and cerebral cortex on MRI. Neuroradiology. 2000;42:781-3. doi: 10.1007/s002340000393.
16. Doss A, Mahad D, Romanowski CA. Wernickeencephalopathy: unusual findings in nonalcoholic patients. J Comput Assist Tomogr. 2003;27:235– 40
17. Theodoreson MD, Zykaite A, Haley M, Meena S. Case of non-alcoholic Wernicke's encephalopathy. BMJ Case Rep. 2019;12:e230763. doi: 10.1136/bcr-2019-230763.
18. Galvin R, Brathen G, Ivashynka A, Hillbom M, Tanasescu R, Leone MA. EFNS guidelines for diagnosis, therapy and prevention of Wernicke encephalopathy. Eur J Neurol. 2010;17:1408–18.