

Wernicke's Encephalopathy After Autologous Stem Cell Transplantation: Case Report

Otolog Kök Hücre Transplantasyonu Sonrası Ortaya Çıkan Wernicke Ensefalopatisi

Fevzi Firat YALNIZ,^a
Çetin ORDU,^b
Özgür KILIÇKESMEZ,^c
Berrin AKTEKİN,^d
S. Sami KARTI^{a,e}

Departments of
^aInternal Medicine,
^cRadiology,
^dNeurology,
^eDivision of Hematology,
Yeditepe University Faculty of Medicine,
^bDivision of Medical Oncology,
Bilim University Faculty of Medicine,
İstanbul

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Yazışma Adresi/Correspondence:
Çetin ORDU
Bilim University Faculty of Medicine,
Department of Internal Medicine,
Division of Medical Oncology, İstanbul,
TÜRKİYE/TURKEY
cetnordu@hotmail.com

ABSTRACT Wernicke's encephalopathy (WE) is an acute neurological condition due to thiamine deficiency. WE due to alcohol abuse or in some other malnutrition and gastrointestinal diseases is well defined. However, WE after allogeneic or autologous stem cell transplantation was defined in only a few cases. Here, we described a patient who experienced acute WE due to prolonged total parenteral nutrition after autologous stem cell transplantation. Early diagnosis with characteristic magnetic resonance imaging changes and low thiamine levels and administration of thiamine lead to dramatic improvement of the patient. In conclusion, should be made differential diagnosis on presentation neurological symptoms and thiamine should be added to long term total parenteral nutrition formulas for prevent WE in stem cell transplantation patients.

Key Words: Wernicke encephalopathy; peripheral blood stem cell transplantation; thiamine; parenteral nutrition, total

ÖZET Wernicke ensefalopatisi (WE) tiamin eksikliğine bağlı gelişen akut nörolojik bir bozukluktur. Alkoliklerde, malnutrisyon ve bazı gastrointestinal hastalıklarda WE iyi tanımlanmıştır, ancak allojenik ve otolog kök hücre transplantasyonu sonrası WE sadece birkaç vakada rapor edilmiştir. Bu olgu sunumunda otolog kök hücre transplantasyonu sonrası uzun süre total parenteral beslenmeye sekonder gelişen WE tanımladık. Magnetik rezonans görüntüleme ve düşük tiamin seviyelerinin serumda gösterilmesinin ardından hastaya Wernicke ensefalopati tanısı konuldu. Tiamin tedavisi başlanan hastanın semptomlarında dramatik bir düzelme gözlemlendi. Uzun süreli total parenteral nütrisyon alan kök hücre transplantasyonu yapılan hastalarda nörolojik semptom görüldüğünde WE'ni ayırıcı tanıya almak gereklidir ve WE'yi önlemek için TPN mayilerine tiamin eklenmelidir.

Anahtar Kelimeler: Wernicke ensefalopatisi; periferik kan kök hücre transplantasyonu; tiamin; parenteral beslenme, total

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Bone marrow transplantation is the treatment of choice for a wide variety of hematological, nonhematological, genetic and immune diseases.¹⁻³ Autologous stem cell transplantation (ASCT) is an effective and potentially curative therapy for different hematological malignancies. However, aside from the neutropenia so the risk of opportunistic infections, conditioning regimens may cause severe side-effects including nausea, vomiting, mucositis and diarrhea leading to a reduced caloric intake and malabsorption.⁴ Administration of commercial total parenteral nutrition (TPN) products become an obligation to overcome these complications. Commer-

cial TPN products does not contain any of vitamin or mineral supplements. Therefore, prolonged commercial TPN administration without additional supplements, could give occasion to certain vitamin or mineral defects.

Thiamin is a water soluble protein and the body can not produce thiamin but must ingest it with the diet. Body stores can be depleted within 4 weeks.⁴ Thiamin deficiency may be manifested as Wernicke's encephalopathy (WE), a serious neurological disorder mostly seen in alcoholics.⁵ Frequently unrecognized, Wernicke's encephalopathy is more prevalent than commonly supposed. Autopsy studies estimate the frequency of Wernicke's encephalopathy to be 0.8-2.8%, suggesting that this treatable disease is substantially underdiagnosed.⁶ WE has been described in many situations other than alcoholism such as hyperemesis gravidarum, gastrointestinal surgery, anorexia nervosa, hemodialysis or peritoneal dialysis, acquired immunodeficiency syndrome, malignancies, and prolonged TPN.

Cases with clinical and radiological evidence of WE have been described during ASCT and allogenic bone marrow transplantation while 10 fatal cases of WE were diagnosed on the basis of autopsy material.⁷ Here we report a patient experienced acute WE after autologous stem cell transplantation associated with prolonged use of TPN.

CASE REPORT

A 58 year old man with relapsed grade III follicular B cell lymphoma was autografted using a regimen with carmustine 300 mg/m² at day -7, etoposide 200 mg/m² from day -6 to -3, cytosine arabinoside (ARA-C) 200 mg/m² from day -6 to -3 twice a day and melphalan 140 mg/m² at day -2. He was put on TPN three days after bone marrow transplantation due to severe nausea, vomiting and oral intolerance. Because of the engraftment failure on day +30, additional stem cells were given to the patient. On day +32 the patient developed nausea and vomiting with head movements. He also suffered from muscle weakness, diplopia, dizziness and mental slowing. On his neurological examination; he was awake, oriented to time, place and per-

son, cooperative without apparent amnesic deficits, but had a slight psychomotor slowing. Bilateral lateral rectus palsy, horizontal nystagmus, gait ataxia with bilateral loss of vibration sensation and paresthesias on distal lower extremities were detected. Motor examination and deep tendon reflexes were normal. Magnetic resonance imaging (MRI) of the brain showed marked hyperintensity of bilateral medial thalami (Figure 1), mammillary bodies on the T2 and FLAIR-weighted sequences. Diffusion-weighted MRI revealed mild diffusion restriction. On the T1-weighted images the lesions were hypointense and there was mild enhancement.

After sampling blood for thiamine level 100 mg thiamine was commenced intravenously. The general condition and neurologic signs of the patient improved dramatically the next day. After 3 days of thiamine administration, the neurological signs and gastrointestinal symptoms disappeared. Thiamine was administered 100 mg per day intravenously for one week followed by oral administration at 50 mg 2 times a day. Thiamine level was found to be 14 ug/L (20-70 ug/L). Two weeks following thiamine treatment control MRI of the brain performed and reported as normal without any sequela of WE.

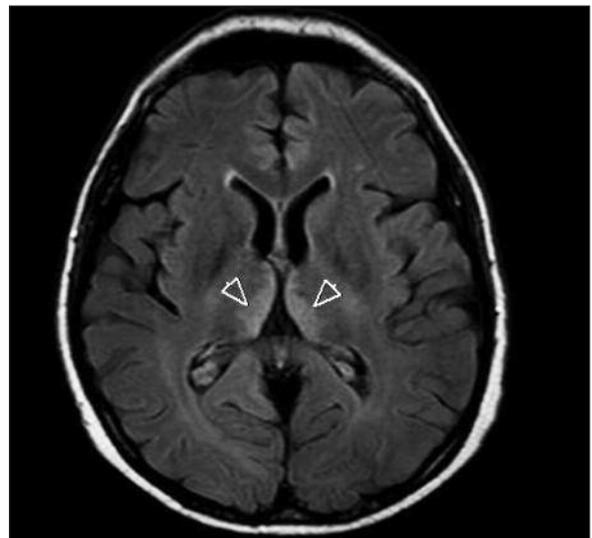


FIGURE 1: Evidence of lesions in thalamic region. Magnetic resonance image (MRI) of the brain; Fluid attenuated inversion recovery MRI demonstrating bilaterally symmetrical hyperintense signals (arrows) in the medial thalami on flair imaging consistent with Wernicke's encephalopathy.

Neutrophil engraftment (absolute neutrophil count $>0.5 \times 10^9/l$) was evident on day +38 and platelet engraftment ($>20 \times 10^9/l$) was reached on day +43 and he was discharged on day +43.

Bone marrow aspirate taken on day +100 showed normal cellularity with no evidence of residual disease. At the last follow-up (9 months after ASCT), complete remission without any sequelae of WE or lymphoma was reported.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

DISCUSSION

Neurological complications are common in patients undergoing ASCT, occurring in 30-39% of cases. These complications may be infectious, cerebrovascular, toxic, immune-mediated, or metabolic. The effect of ASCT and allo-SCT on nutritional status may be different. TPN is not routinely administered to ASCT patients unless complications occur, such as prolonged mucositis. This condition represents one of the main indications for artificial nutrition in patients undergoing ASCT. Neutrophil and platelet engraftment occur around median 10. and 13. day of transplantation respectively.⁸ Although both the severity and the duration of gastrointestinal toxicity may differ greatly among individuals, the condition significantly affects food intake and absorption for up to 2-3 week after ASCT.⁹

As far as we know there are only 3 cases of WE after ASCT and only one case after autologous bone marrow transplantation.¹⁰⁻¹³ However, 10 fatal cases of WE were diagnosed on the basis of autopsy material from out of 180 cases.⁷ This may show that WE is more prevalent than commonly supposed.

Thiamine is a water soluble vitamin. This compound is phosphorylated to a coenzyme form, thiamine pyrophosphate (TPP) which serves as a coenzyme in many alpha- ketoacid decarboxylation and transketolation reactions. Inadequate thi-

amine availability leads to impairments of the foregoing reactions, resulting in inadequate adenosine triphosphate synthesis and abnormal carbohydrate metabolism.^{14,15} Primary thiamine deficiency is commonly due to a diet of highly refined carbohydrates. In conditions with increased carbohydrate intake for example during long term TPN and glucose containing intravenous solution usage cause increased demand for thiamine for proper carbohydrate metabolism.¹⁶

Thiamine (vitamin B-1) deficiency can result in WE, a serious neurologic disorder. The three components of the classic triad of Wernicke encephalopathy are encephalopathy, gait ataxia and ophthalmoplegia.¹⁷ However, clinically only 16% of cases presented with this triad.¹⁸ Considering the low incidence of WE, variable and nonspecific symptoms, early diagnosis with MRI of the brain is obligatory.¹⁹

Magnetic resonance imaging (MRI) offers the best way to make a definitive diagnosis. Although the clinical evidence for the utility of MRI is based on a study in which sample size was small, the reported sensitivity of MRI was 53% and specificity was 93% for both acute and chronic WE.¹⁹ The appearance of acute WE on MRI demonstrates abnormal hyperdensity of the mamillary bodies and periaqueductal gray matter with associated abnormal enhancement on T1-weighted images.²⁰

In our patient the deficit observed on +32 of ASCT, on 28th day of TPN. We normally prefer TPN solutions in stem cell transplantation patients and this is the first case we came across with WE in our clinic. Because of the engraftment failure and severe mucositis this patient could not eat food for a long time. High caloric intake with TPN solutions could not opposed with adequate amount of thiamine.

In conclusion, WE should be considered among the neurological complications after stem cell transplantation. When oral intake of the patient is delayed TPN formulas should be supplemented with multivitamin preparations including thiamine.

REFERENCES

- Blaise D, Bay JO, Faucher C, Michallet M, Boiron JM, Choufi B, et al. Reduced-intensity preparative regimen and allogeneic stem cell transplantation for advanced solid tumors. *Blood* 2004;103(2):435-41.
- La Nasa G, Giardini C, Locatelli F, Argioli F, Vassallo E, Prete A, et al. Italian Bone Marrow Transplant Group (GITMO). Unrelated bone marrow transplantation in thalassemia. The experience of the Italian Bone Marrow Transplant Group (GITMO). *Haematologica* 2002;87(8 Suppl):58-61.
- de Buys P, Khanna D, Furst DE. Hemopoietic stem cell transplantation in rheumatic diseases--an update. *Autoimmun Rev* 2005;4(7):442-9.
- Sullivan KM. Complications of bone marrow transplantation. In: Hoffman R, Benz EJ Jr, Shattil SJ, eds. *Hematology-Basic Principles and Practise*. 1st ed. Philadelphia: Churchill Livingstone; 1991. p. 242-9.
- Thiamine. Monograph. *Altern Med Review* Feb 2003;8(1):59-62.
- Thomson AD, Cook CC, Touquet R, Henry JA; Royal College of Physicians, London. The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and Emergency Department. *Alcohol Alcohol* 2002;37(6):513-21.
- Bleggi-Torres LF, de Medeiros BC, Werner B, Neto JZ, Loddo G, Pasquini R, et al. Neuropathological findings after bone marrow transplantation: an autopsy study of 180 cases. *Bone Marrow Transplant* 2000;25(3):301-7.
- Gonçalves TL, Benvegnú DM, Bonfanti G. Specific factors influence the success of autologous and allogeneic hematopoietic stem cell transplantation. *Oxid Med Cell Longev* 2009;2(2):82-7.
- Keenan AM. Nutritional support of the bone marrow transplant patient. *Nurs Clin North Am* 1989;24(2):383-93.
- Majolino I, Caponetto A, Scimé R, Vasta S, Fabbiano F, Caronia F. Wernicke-like encephalopathy after autologous bone marrow transplantation. *Haematologica* 1990;75(3):282-4.
- Messina G, Quartarone E, Console G, Irrera G, Martino M, Pucci G, et al. Wernicke's encephalopathy after allogeneic stem cell transplantation. *Tumori* 2007;93(2):207-9.
- Baek JH, Sohn SK, Kim DH, Kim JG, Lee HW, Park SP, et al. Wernicke's encephalopathy after allogeneic stem cell transplantation. *Bone Marrow Transplant* 2005;35(8):829-30.
- Bleggi-Torres LF, de Medeiros BC, Ogasawara VS, Loddo G, Zanis Neto J, Pasquini R, et al. Iatrogenic Wernicke's encephalopathy in allogeneic bone marrow transplantation: a study of eight cases. *Bone Marrow Transplant* 1997;20(5):391-5.
- Beers MH, Berkow R, Bogin RM. Wernicke Korsakoff Syndrome. *The Merck Manual*. 17th ed. Whitehouse Station, NJ: Merck & Co; 1999. p.1383-4.
- Cole PD, Kamen BA. "Beriberi" interesting! *J Pediatr Hematol Oncol* 2003;25(12):924-6.
- McCormick DB, Shils ME, Young VR. Thiamin, riboflavin, niacin, vitamin B6, pantothenic acid and biotin. *Modern Nutrition in Health and Disease*. Philadelphia, PA: Lea and Febiger; 1988. p.355-61.
- Donnino MW, Vega J, Miller J, Walsh M. Myths and misconceptions of Wernicke's encephalopathy: what every emergency physician should know. *Ann Emerg Med* 2007;50(6):715-21.
- Victor M, Adams RD, Collins GH. *The Wernicke-Korsakoff Syndrome and Related Neurologic Disorders Due to Alcoholism and Malnutrition*. 1st ed. Philadelphia: FA Davis Company; 1988. p.1-231.
- Antunez E, Estruch R, Cardenal C, Nicolas JM, Fernandez-Sola J, Urbano-Marquez A. Usefulness of CT and MR imaging in the diagnosis of acute Wernicke's encephalopathy. *AJR Am J Roentgenol* 1998;171(4):1131-7.
- Kaineg B, Hudgins PA. Images in clinical medicine. Wernicke's encephalopathy. *N Engl J Med* 2005;352(19):e18.