

Bakır Eksikliği ile Subakut Kombine Dejenerasyonun Birlikte Görüldüğü Atipik Bir Vaka

An Atypical Case of Subacute Combined Degeneration With Concomitant Copper Deficiency

Onur Engin, Ali Karakaş, Banu Dilek, Özlem El

Dokuz Eylül Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, İzmir, Türkiye

ÖZ

Giriş: Subakut kombine dejenerasyon (SKD) kobalamin eksikliğinden kaynaklanan nörodejeneratif bir hastalıktır. B12 vitamini eksikliğine bağlı olarak diğer nörolojik, psikiyatrik, hematolojik ve gastrointestinal semptomlar eşlik edebilir. Bu yazıda vitamin B12 eksikliğinin yanında bakır eksikliği de bulunan atipik subakut kombine dejenerasyon olgusunu sunmaktayız.

Vaka Sunumu: 74 yaşında kadın hasta fiziksel tıp ve rehabilitasyon departmanına her iki bacakta güçsüzlük ve yürüyememe şikayeti ile başvurdu. Her iki alt ekstremitede belirgin güçsüzlüğü vardı ve sol yanlı dismetrisi ve disdiadochokinezi mevcuttu. Alt ekstremitelerde vibrasyon, pozisyon duygusu kaybı, iki nokta ayırımı bozulmuştur. Kliniğimize başvurmadan önce B12 vitamini replase edilmişti. Hastanın semptomları replasmana rağmen progrese olmaya devam etti. Spinal MR görüntülemeye spinal kord kompresyonuna veya miyelopatiye rastlanmadı. İğne EMG de motor ünite rekrütmanında azalma saptandı. Üst gastrointestinal siste endoskopisinde B12 eksikliği ile uyumlu olarak kronik atrofik gastrit saptandı. Hastanın bakır düzeyi düşüktü. Tedaviye oral bakır eklendi. Hasta 6 ve 9. aylarda değerlendirildi. Fonksiyonel durumu bir önceki vizitle aynıydı.

Sonuç: B12 vitamini tedavisine yanıtız miyelopatide bakır eksikliğini göz önünde bulundurmak öneml

Anahtar Kelimeler: subakut kombine dejenerasyon, B12 vitamini eksikliği, bakır eksikliği

ABSTRACT

Background: Subacute combined degeneration (SCD) is a neurodegenerative disease caused by cobalamin deficiency. It is can be accompanied by other neurological, psychiatric, hematological and gastrointestinal symptoms. Here we describe a patient with subacute combined degeneration who has vitamin B12 and copper deficiency.

Case Description: 74-year-old woman was admitted to our physical medicine and rehabilitation department complaining of weakness in both legs and inability to walk. She had marked loss of strength in both lower extremities also dysmetria and dysdiadochokinesia tests were positive on left-side. Vibration, position sense, two-point discrimination were impaired in the lower extremities. Her vitamin B12 was replaced before admission to our department. Patient's symptoms kept progressing despite the vitamin replacement. Her spinal MRI showed no compression of spinal cord or myelopathy. The needle EMG findings revealed a decrease in motor unit recruitment. Upper gastrointestinal endoscopy revealed chronic atrophic gastritis which is compatible with B12 deficiency. Her blood copper level was low. Oral copper was added to the treatment. Patient evaluated on 6th and 9th months after discharge. Her functional state was similar with previous visit.

Conclusion: It is important to consider copper deficiency in patients with myelopathy who are unresponsive to vitamin B12 treatment

Key words: subacute combined degeneration, vitamin B12 deficiency, copper deficiency

İletişim / Correspondence:

Dr. Onur Engin

Dokuz Eylül Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, İzmir, Türkiye

E-mail: oengin4@hotmail.com

Başvuru Tarihi: 18.03.2018

Kabul Tarihi: 30.09.2018

INTRODUCTION

Subacute combined degeneration (SCD) is a neurodegenerative disease caused by cobalamin deficiency. It can be accompanied by other neurological, psychiatric, hematological and gastrointestinal symptoms (1). Malabsorption, malnutrition and a genetic deficiency of the methylmalonyl-Coa mutase can give rise to vitamin B12 deficiency (2). Subacute combined degeneration after nitrous oxide exposure due to anesthesia and nitrous oxide abuse is also reported in rare cases(3,4).

Additionally, copper deficiency may present with neurologic deficits similar to that is seen in patients with subacute combined degeneration (5). Copper deficiency may also involve multiple organ systems. It has hematological, neurological and cardiovascular effects(6). Copper deficiency reported to have a range of neurological manifestations such as myelopathy, peripheral neuropathy(7).

Here we describe a patient with subacute combined degeneration who has vitamin B12 and copper deficiency.

CASE REPORT

A 74-year-old woman was admitted to our department in December, 2015 with weakness in both legs and inability to walk. She reported progressive weakness and balance problems over 5 years. The patient was examined in neurology department and diagnosed as subacute combined degeneration due to vitamin B12 deficiency before admission. The patient also diagnosed as essential thrombocytosis 5 years ago. Her medical and surgical history was unremarkable. Upon examination, she was alert and well oriented. Her mental status was normal but her rate of speech was slow. Her upper extremity muscle strength was normal but the motor exam showed power of 4-/5 in lower extremities. She exhibited marked spasticity on hip adductors. Neurological examination revealed dysmetria and dysdiadochokinesia on left-side. Deep tendon reflexes were normoactive bilaterally in upper extremities while patellar and ankle reflexes were increased symmetrically. Vibration, position sense, two-point discrimination were impaired over the lower limbs. On sensory

examination she reported having hypoesthesia on distal lower limb but did not address a certain dermatome. Babinski sign were present on both sides. She denied having fecal incontinence but she reported urge urinary incontinence. The patient was able to sit when assisted, however she had difficulty in sitting unsupported. Peripheral pulses were palpable. Lower extremity venous and arterial doppler sonography was normal. Grade 2-3 hepatic steatosis and increase trabeculations in bladder were detected on abdominal ultrasonography. Laboratory investigations revealed macrocytic anemia(Hgb:11.2 g/dl (N:12-16), Mcv:120.7 fl (N:80.7-95.5),Mch:37.8 pg (N:27.2-33.5)), lack of vitamin D (25-OH D vitamin:12.43 (n:30-100)) and mild hypertriglyceridemia (Triglyceride: 231 (N:0-200)). Blood tests showed a low serum vitamin B12 level of 87 pg/ml. Vitamin B12 level became 299 pg/ml after replacement (N:126.6-505) . Additionally, her serum folic acid level and plasma homocystein level was normal. Weekly 50,000 IU VIT D-3 replacement started in terms of vitamin D deficiency. Physical examination and laboratory results were consistent with subacute combined degeneration secondary to vitamin B12 deficiency. But her neurological condition continued to deteriorate despite the cobalamin replacement. To this end, brain MRI, cerebrospinal fluid(CSF) flow MRI and whole spinal MRI were performed. Spinal MRI showed discal herniation but no compression of spinal cord or myelopathy was detected (figure 1,2,3).



Figure 1. Spinal MRI T2 sagittal imaging (cervical part)

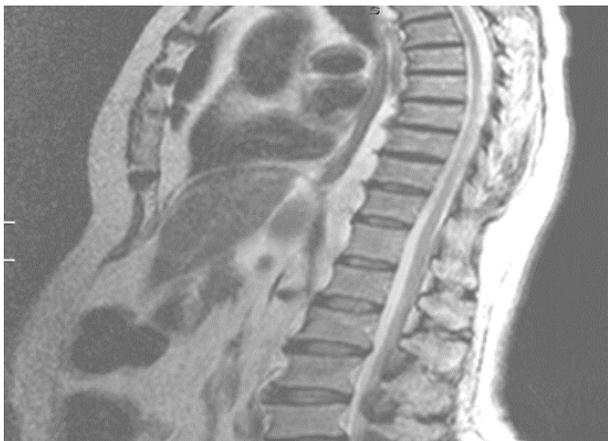


Figure 2. Spinal MRI T2 sagittal imaging (thoracic part)

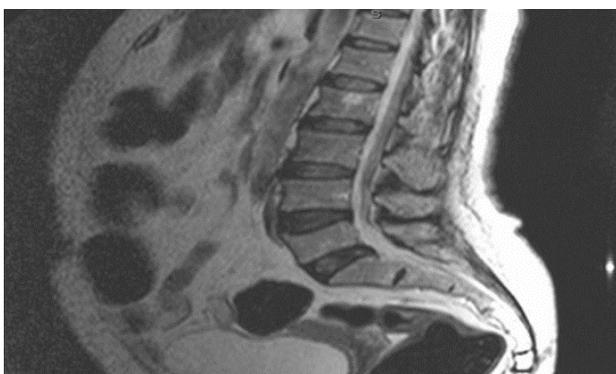
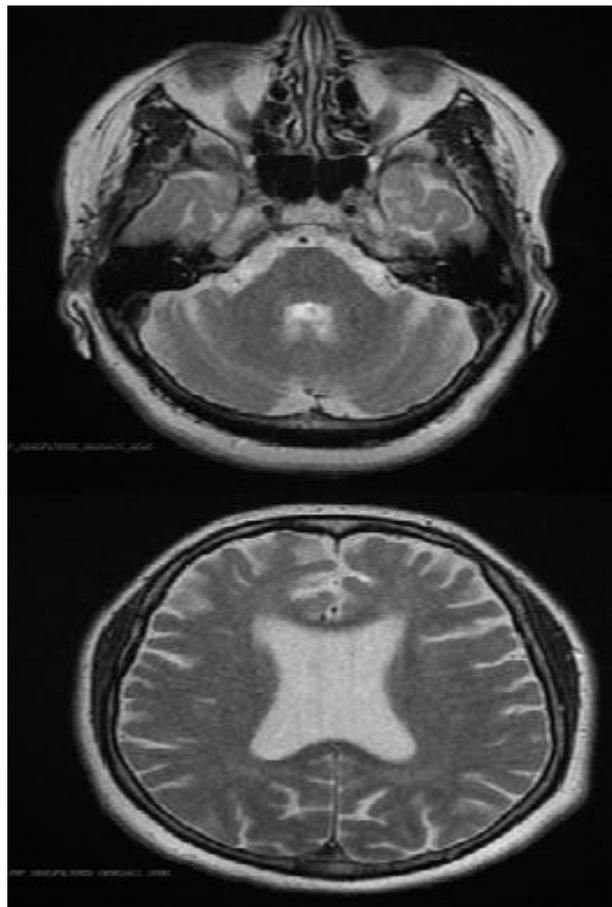


Figure 3. Spinal MRI T2 sagittal imaging (lumbar part)

Cerebral and cerebellar atrophy was seen on brain MRI (figure 4,5). CSF flow MRI was normal. EMG findings were normal except a decrease in motor unit recruitment. Upper gastrointestinal endoscopy revealed chronic atrophic gastritis which is compatible with B12 deficiency. The serum copper level was 79,7 mg / dL (N79-155) and ceruloplasmin level was 18.4 mg / dL (N: 20-60), and 24-hour urine copper was 8.7 (N 3 - 35). Oral copper supplements has been added to the treatment. The patient was discharged after 27 sessions of physical therapy and rehabilitation program, and was advised continuing program in an outpatient setting. Patient evaluated on 6th and 9th months after discharge. Her functional state was similar with previous visits.



Figures 4 and 5. Brain MRI Axial T2 imaging

DISCUSSION

Cobalamin is a cofactor for two enzymes that is present in mammalian cells: mitochondrial 1-methylmalonyl-coenzyme A (CoA) mutase (MCM) and cytoplasmic homocysteine methyltransferase(8). These enzymes are important for DNA and cell metabolism so a deficiency of Vitamin B12 may give rise to disruption of DNA related and cellular mechanisms that results in serious clinical consequences.

Vitamin B12 deficiency may manifest in multiple organ systems and it is defined as plasma or serum vitamin b12 concentration lower than 148 pmol/L (200 pg/mL) (9). Serum (or less commonly, urinary) methylmalonic acid (MMA), total homocysteine, holotranscobalamin can also be used for diagnosing this vitamin deficiency (10). SCD patients may have normal or elevated serum B12 levels which is termed “functional vitamin B12 deficiency”.

It has been reported that SCD patients with normal or elevated serum B12 levels had abnormal transcobalamin (TC), a factor that plays a role in cellular uptake of B12. Transcobalamin deficiency causes megaloblastic anemia in infants with normal cobalamin concentrations. Vitamin B12 deficiency may be secondary to vitamin B12 intake, autoimmune disorders, gastric surgery malabsorption and drugs (11). Deficiency state results in decreased activity of cobalamin-dependent methylcobalamin esterase enzyme with the resultant elevated levels of methylmalonic acid, which is toxic to myelin (12).

The bone marrow is most commonly affected system due to vitamin B12 deficiency. Anaemia may range from mild to severe, with symptoms of fatigue, dyspnea, palpitations, and pallor. All cell lines can be affected, with macrocytic anaemia, low white cell count or neutropenia, and thrombocytopenia(13). Neurologically it affects the spinal cord, peripheral nerves, optic nerve, and brain (14,15). Patients may present sensory abnormalities, weakness, gait ataxia or cognitive impairment (16).

Subacute combined degeneration is a progressive myelopathy that can be associated with neurologic deficits such as sensory abnormalities, ascending paresthesias, weakness, ataxia, loss of sphincter control, and gait disturbances (17,18,19). According to a study which documents 23 cases with SCD, all patients gradually displayed limb weakness, gait ataxia, mental disorders or cognitive impairment, blurred vision, defecation abnormalities or impotence and other symptoms. Their data showed that the patients' chief complaints and neurological signs were not totally consistent and the neurological signs might be more apparent than symptoms. Apart from the neurological and hematological involvement, cobalamin deficiency can result in skin changes, reproductive system disturbances, osteoporosis and rarely cardiomyopathy(13)

MRI may be helpful for the diagnosis of subacute combined degeneration. Typically the T2WI demonstrates hyperintense lesions in the posterior column (with inverted V sign) , rarely lateral column and brain stem may also be affected.

Lesions typically exist on cervical and upper thoracic part of the spinal cord. On MRI, several patterns were described: focal or small cord lesions involving few contiguous levels, extensive linear abnormalities and scattered small multifocal lesions(19). Although unusual, cases with anterior cord involvement has been described(20). In a study which includes a total 54 patients with biochemically proven vitamin B12 deficiency , MRI showed cord signal abnormality in only 8 patients out of 54 patients with low sensitivity of 14.8% (21). Jaisi et al reported 26.09%(6/23) of their patients were found having spinal cord lesions on MRI, where as 82.00% reported by Locatelli et al (22). The patient herein described also had no MRI abnormality targeting myelopathy. The reasons why there is no MRI finding maybe as follows: first, MRI changes may lag after the onset of clinical symptoms .Second, conventional MRI has poor sensitivity to detect microstructural changes in SCD, for this reason diffusion tensor imaging is a good alternative(21). Lastly, MRI damages of SCD are not present in every patient.

Standard initial treatment is 1000 µg hydroxocobalamin intramuscularly three times a week for two weeks in patients without neurological involvement. If there are neurological symptoms, according to the British National Formulary recommendations 1000 µg hydroxocobalamin intramuscularly on alternate days should be continued for two weeks until there is no further improvement (23).

A study of 57 cases with subacute combined degeneration reported that After initiation of B12 therapy, 49(86%) patients improved and 8 (14%) had complete resolution of signs and symptoms (19).

Copper deficiency may also involve multiple organ systems. It has hematological, neurological and cardiovascular effects(6). Copper deficiency reported to have a range of neurological manifestations such as myelopathy, peripheral neuropathy(7). Patients may present with sensory ataxia due to copper deficiency myelopathy which represents an often underdiagnosed, acquired neurological syndrome (24). Similar to subacute combined degeneration, copper deficiency

myelopathy is characterized by posterior column dysfunction. The known causes of the copper deficiency include gastrointestinal surgery, malabsorption, excessive zinc ingestion, overuse of zinc-containing denture adhesive or iron overload (25,26). Oftentimes no exact etiology can be revealed. Our patient has sensory ataxia and peripheral neuropathic symptoms which is consistent with both CDM and SCD. Her symptoms were progressing under vitamin B12 treatment. After initiating oral copper supplements her functional level was similar with previous visit.

In conclusion, it is important to consider copper deficiency in patients with myelopathy who is unresponsive to vitamin B12 treatment.

REFERENCES

1. Reynolds E. Vitamin B12, folic acid, and the nervous system. *Lancet Neurol.* 2006;5:949–60.
2. Miscusi M., Testaverde L., Rago A., Raco A., Colonnese C. Subacute combined degeneration without nutritional anemia. *J Clin Neurosci.* 2012 Dec;19(12):1744-5.
3. Beltramello A, Puppini G, Cerini R, El-Dalati G, Manfredi M, Roncolato G et al Subacute combined degeneration of the spinal cord after nitrous oxide anaesthesia: role of magnetic resonance imaging. *J Neurol Neurosurg Psychiatry.* 1998 Apr;64(4):563-4.
4. Pugliese RS, Slagle EJ, Oettinger GR, Neuburger KJ, Ambrose TM. Subacute combined degeneration of the spinal cord in a patient abusing nitrous oxide and self-medicating with cyanocobalamin. *Am J Health Syst Pharm.* 2015;72(11):952–7.
5. Kumar N., Gross J. B., Jr., Ahlskog J. E. Copper deficiency myelopathy produces a clinical picture like subacute combined degeneration. *Neurology.* 2004;63(1):33–9.
6. Jaiser SR, Winston GP. Copper deficiency myelopathy. *J Neurol.* 2010;257(6):869-81.
7. Kumar N, Crum B, Petersen RC, Vernino SA, Ahlskog JE. Copper deficiency myelopathy. *Arch Neurol* 2004;61(5):762–6
8. Banerjee R., Ragsdale S.W. The many faces of vitamin B12: Catalysis by cobalamin-dependent enzymes. *Annu. Rev. Biochem.* 2003;72:209–47.
9. Allen L.H. How common is vitamin B-12 deficiency? *Am. J. Clin. Nutr.* 2009;89:693S–696S.
10. Hvas AM, Nexø E. Diagnosis and treatment of vitamin B12 deficiency—an update. *Haematologica.* 2006;91:1506–12.
11. Shipton MJ, Thachil J. Vitamin B12 deficiency – A 21st century perspective. *Clin Med.* 2015;15(2):145–50.
12. Srikanth SG, Jayakumar PN, Vasudev MK, Taly AB, Chandrashekar HS. MRI in subacute combined degeneration of spinal cord: a case report and review of literature. *Neurol India* 2002; 50(3):310-2.
13. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. *BMJ.* 2014;349:g5226.
14. Puri V, Chaudhry N, Goel S, Gulati P, Nehru R, Chowdhury D. Vitamin B12 deficiency: A clinical and electrophysiological profile. *Electromyogr Clin Neurophysiol.* 2005;45:273–84.
15. Aaron S., Kumar S., Vijayan J., Jacob J., Alexander M., Gnanamuthu C. Clinical and laboratory features and response to treatment in patients presenting with vitamin B12 deficiency-related neurological syndromes. *Neurol India.* 2005;53(1):55–8.
16. Li, J, Ren M, Dong A, Wu Y, Han N, Deng B, et al A retrospective study of 23 cases with subacute combined degeneration, *Int Journal Neurosci,* 126:10, 872-7
17. Scalabrino G. Cobalamin (vitamin B12) in subacute combined degeneration and beyond: traditional interpretations and novel theories. *Exp Neurol.* 2005;192(2):463–79
18. Scalabrino G (2001) Subacute combined degeneration one century later. The neurotrophic action of cobalamin (vitamin B12) revisited. *J Neuropathol Exp Neurol* 60: 109-20
19. Vasconcelos OM, Poehm EH, McCarter RJ, Campbell WW, Quezado ZMN. Potential Outcome Factors in Subacute Combined Degeneration: Review of Observational Studies. *J Gen Intern Med.* 2006;21(10):1063-8.
20. Briani, C., Dalla Torre, C., Citton, V., Manara, R., Pompanin, S., Binotto, G. et al. Cobalamin Deficiency: Clinical Picture and Radiological Findings. *Nutrients.* 2013;5(11), 4521–39.
21. Jain KK, Malhotra HS, Garg RK, Gupta PK, Roy B, Gupta RK. Prevalence of MR imaging abnormalities in vitamin B12 deficiency patients presenting with clinical features of subacute combined degeneration of the spinal cord. *J Neurol Sci* 2014;342(1–2):162–6.

22. Locatelli ER, Laurenno R, Ballard P, Mark AS. MRI in vitamin B12 deficiency myelopathy. *Can J Neurol Sci.* 1999;26:60–3.

23. Devalia, V., Hamilton, M. S., Molloy, A. M. and the British Committee for Standards in Haematology (2014), Guidelines for the diagnosis and treatment of cobalamin and folate disorders. *Br J Haematol*, 166: 496–513.

24. Plantone D, Primiano G, Renna R, et al. Copper deficiency myelopathy: A report of two cases. *The Journal of Spinal Cord Medicine.* 2015;38(4):559-62.

25. Doherty K, Connor M, Cruickshank R. Zinc-containing denture adhesive: a potential source of excess zinc resulting in copper deficiency myelopathy. *Br Dent J.* 2011;210(11):523–5.

26. Klevay LM. Iron overload can induce mild copper deficiency. *J Trace Elem Med Biol.* 2001;14(4):237–40.