Constellation of Cognitive Impairment, Spasticity, and Lower Motor Neuron Disease Secondary to Possible Whipple Disease

Ceren Aliş, Ayşegül Gündüz, Güneş Kızıltan, Hülya Apaydın

Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Cite this article as: *Aliş C, Gündüz A, Kızıltan G, Apaydın H. Constellation of Cognitive Impairment, Spasticity, and Lower Motor Neuron Disease Secondary to Possible Whipple Disease. Cerrahpaşa Med J 2021; 45(1): 49-52.*

Abstract

Herein, we report a patient with dementia, parkinsonism, and motor neuron disease owing to possible central nervous system involvement of Whipple disease. Although co-existence of dementia, parkinsonism, and second-order motor neuron involvement may be seen in some degenerative disease complexes, excluding a reversible condition is a necessity. The critical issue in diagnosing our patient was the presence of gastroparesis and arthritis in history associated with progressive supranuclear palsy-like clinical features. Impairment in any domain of cognition may be observed in Whipple disease. Our patient had prominent attention and memory deficits. To our knowledge, this is the first case of generalized lower motor neuron involvement with cognitive deficits and parkinsonism in Whipple disease.

Keywords: Cognitive impairment, dementia, parkinsonism, second motor neuron, Whipple disease

Olası Whipple Hastalığına Bağlı Bilişsel Bozukluk, Spastisite ve Alt Motor Nöron Hastalığı

Öz

Burada, olası Whipple hastalığının santral sinir sistemi tutulumuna ikincil demans, parkinsonizm ve motor nöron tutulumu bulguları ile başvuran bir hastayı sunduk. Demans, parkinsonizm ve ikinci motor nöron tutulumuyla giden bazı dejeneratif hastalık kompleksleri görülebilse de, geri dönüşümlü bazı tabloları ayırt etmek gereklidir. Hastamızın tanısındaki kritik noktalar gastroparezi ve artrit öyküsü ile birlikte progresif supranükleer felç benzeri klinik özellikler olmasıydı. Whipple hastalığında kognisyonun herhangi bir bileşeninde etkilenim görülebilir. Olgumuzda ön planda dikkat ve hafıza etkilenimi vardı. Literatür incelendiğinde bu vaka yaygın ikinci motor nöron tutulumu, kognitif yıkım ve parkinsonizm ile ortaya çıkan ilk Whipple hastalığı vakasıdır.

Anahtar kelimeler: Whipple hastalığı; demans; parkinsonizm; ikinci motor nöron; kognitif yıkım

Tropheryma whipplei (*T. whipplei*) is a bacteria, which can cause chronic infection in humans with symptoms such as arthralgia, diarrhea, fever, and weight loss. Central nervous system (CNS) involvement can be seen in patients with systemic disease or it can be the first manifestation [1, 2]. CNS involvement in Whipple disease can present with numerous symptoms and signs such as nuchal rigidity, seizures, cognitive impairment, oculomasticatory myorhythmia, myoclonus, chorea, supranuclear palsy, and ophthalmoplegia [1, 2]. Although rare, peripheral nervous system involvement was reported and confirmed by biopsy [3].

Herein, we aimed to report a patient with possible Whipple disease, which was progressive in two years with cognitive impairment, parkinsonism, pyramidal signs, and second-order motor neuron disease and showed dramatic improvement after antibiotics.

Case Presentation

Written informed consent was obtained from patient. A 61-year-old male patient with a clinical picture reminiscent of advanced-stage progressive supranuclear palsy (PSP) and 2-year history of progressive speech disorder, memory problems, and gait disturbance was admitted to our outpatient clinic. At first, he had a gait abnormality described as leg stiffness, which was accompanied by muscle wasting and weakness. Within months, small-stepped gait appeared, and his symptoms rapidly worsened. Because he had findings suggesting parkinsonism, he had a trial of levodopa for several weeks without any

This case report was reported as a poster in 52nd National Neurology Congress.
Received/Geliş Tarihi: 08.08.2020 **Accepted/Kabul Tarihi:** 07.01.2021
Available Online Date/ Çevrimiçi Yayın Tarihi: 22.02.2021
Address for Correspondence/Yazışma Adresi: Ceren Aliş, Department of Neurology, İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey
E-mail/E-posta: cerencivcik@gmail.com
DOI: 10.5152/cjm.2021.20026

improvement. On neurologic examination at admission, 2 years after the symptom onset, he was awake, but communication was limited due to severe dysarthria. He had restricted upward gaze, generalized muscle weakness and atrophy with fasciculations, spasticity, rigidity at axial and bilateral appendicular joints, hypokinetic dysarthria, and myoclonus at distal parts of extremities. In minimental state examination test, he was unable to write or make a drawing probably because of appendicular weakness and parkinsonism. However, he had deficits in orientation and attention and had short-term memory. He was disoriented at time and place, whereas person orientation was normal. He had prominent working memory deficit.

He had a history of type-2 diabetes mellitus, which was well controlled with oral antidiabetics. He had dyspepsia and bloating since the gastric ulcer operation in 1991. He was diagnosed with seronegative arthritis 3 years before the admission when he had complaints attributed to arthritis. Brain magnetic resonance imaging (MRI) revealed cerebral atrophy, and electroencephalogram (EEG) showed diffuse slowing. No abnormality was found in the MRI examination of the spinal cord. Because of wasting and fasciculations, electromyography was performed confirming second motor neuron involvement with fasciculations and fibrillation potentials. There was no family history of infectious diseases, malignancy, or degenerative diseases. Although the investigations continued, about 3 months after the first referral, the patient was hospitalized with fever, disorientation, and confusion. Although he had axial rigidity, neck stiffness and meningitis was suspected. Cerebrospinal fluid (CSF) analysis was performed. CSF glucose level was 66 mg/dL, and the blood glucose level was 164 mg/dL.

Additionally, there was a marked increase in CSF protein with 213 mg/dL and 60 leukocytes, of which 60% were neutrophils. Polymerase chain reaction (PCR) assays for viral diseases, Mycobacterium tuberculosis, and T. whipplei as well as culture for tuberculosis were all negative.

Successive investigations for paraneoplastic, neoplastic, infectious, and rheumatological diseases, including CSF test, were performed without a final diagnosis. Tests for vitamin B12, HIV, syphilis antibodies, thyroid dysfunction, vasculitis markers, paraneoplastic disorders, celiac disease, anti-glutamic acid decarboxylase antibodies, protein electrophoresis, immunoelectrophoresis, and tumor markers were all negative.

Considering CSF findings, severe gastroparesis and seronegative arthritis in the history, CNS infections were quite likely, in which CNS tuberculosis and Whipple disease were the leading ones. Because of high frequency in our country, tuberculosis considered first. However, because of the absence of any pathological systemic and lung involvement signs and the presence of normal imaging findings, the diagnosis was excluded. Gastrointestinal endoscopic small bowel biopsy was planned for Whipple disease. However, it was impossible to perform because of the lack of gastric emptying because of gastroparesis.

Parenteral ceftriaxone (for 2 weeks) with rifampicin, isoniazid, pyrazinamide, and ethambutol treatment, which might be useful in both tuberculosis and Whipple disease, was started. Unfortunately, PCR studies for Whipple disease was performed approximately 15 days after the initiation of antibiotics owing to technical and social factors. After starting this therapy, within 20 days, conspicuous improvement was observed in the spasticity, muscle weakness, and parkinsonism in his upper extremities, and speech became more comprehensible. In the first 6 months under the treatment, his cognition and speech was almost normal, and he became able to use his hands, although unable to walk owing to spasticity and weakness in his legs. However, he was able to walk with one crutch in the first-year follow-up with a year-long treatment.

Discussion

Our patient had neurologic symptoms attributed to involvement of the extrapyramidal, upper and lower motor neuron, and cognitive systems. Degenerative diseases, including corticobasal degeneration, frontotemporal dementia (FTD)-amyotrophic lateral sclerosis complex, PSP, and Lewy body dementia (LBD), may lead to various clusters of these symptoms. However, rapid deterioration in the second year with high fever and neck stiffness was unexpected for degenerative disorders. Therefore, detailed tests were performed for infections, neoplastic/paraneoplastic, and autoimmune diseases. Among infections, tuberculosis, neurosyphilis, prion diseases, and Whipple disease were included in the differential diagnosis because they may mimic various Parkinson plus syndromes. Neurosyphilis was excluded using the serologic test. Prion diseases were eliminated by the absence of specific findings successive EEG or brain MRI investigations. Among infections, tuberculosis and Whipple disease, which may cause subacute-chronic course, were investigated in our patient.

Whipple disease is a rare multisystem chronic infectious disease. Although classical clinical symptoms are gastrointestinal problems, weight loss, and joint complaints, it may even present as isolated CNS involvement [1, 2]. Common CNS presentations of Whipple disease are headache, seizures, and sometimes meningoencephalitis; however, it can mimic any neurological condition. In diagnosing Whipple

disease, it is crucial to identify DNA of bacteria by PCR in CSF or other tissues [1, 4, 5]. CSF sample of our patient was negative probably because it was performed weeks after the initiation of antibiotic therapy, especially ceftriaxone. However, the critical issue in the diagnosis of our patient was the presence of gastroparesis and arthritis in the history, because they occur in almost 70% of cases with Whipple disease. The rapidly PSP-like clinical picture in a few months with prominent limitation of the vertical eye movements and symmetric advanced parkinsonism without structural MRI lesion led us to include Whipple disease in the differential diagnosis list. Even without a tissue or serological finding, we presumed our patient as a case of "possible Whipple disease" according to the diagnostic criteria described by Hurth et al. [6] with the supportive contribution of systemic features.

Presence of upper and lower motor neuron findings together with cognitive and extrapyramidal findings in Whipple disease is relatively rare. However, the diagnosis was possible without development of meningoencephalitis if systemic findings were considered. A delay of 1–10 years after the onset of the systemic disease until the onset of nervous system involvement was reported in the literature [1].

Impairment in any domain of cognition may be observed. There are case reports of FTD-like symptoms [7, 8], isolated prosopagnosia [9] or anterograde amnesia with odd behavior, confabulation, and delusional thinking [10]. Severe motor symptoms hindered a thorough neuropsychological analysis in our patient, but he clearly had attention and memory problems with relatively preserved language. In literature, there are reports of Whipple disease mimicking LBD or PSP [5, 6, 11]. Myelitis has also been reported in Whipple disease [12]. However, to our knowledge, such a generalized lower motor neuron involvement was not reported. As mentioned above, questioning systemic features is crucial in identifying Whipple disease, a treatable and reversible disorder.

We think the improvement started after using ceftriaxone. However, long-term treatment with rifampicin for 1–2 years is required to prevent recurrences, which was done in our patient.

In conclusion, in the constellation of symptoms that may be attributed to the involvement of the CNS and peripheral nervous system and associated gastroparesis and arthritis, Whipple disease should be considered.

Informed Consent: Written informed consent was obtained from patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.G.; Design – A.G., C.A.; Supervision – A.G., G.K., H.A.; Data Collection and/or Processing – C.A., A.G.; Analysis and/or Interpretation – A.G., G.K., H.A.; Literature Search – C.A.; Writing Manuscript – C.A., A.G.; Critical Review – G.K., H.A.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Hasta Onamı: Yazılı hasta onamı bu olguya katılan hastadan alınmıştır.

Hakem Değerlendirmesi: Dış bağımsız.

Yazar Katkıları: Fikir – A.G.; Tasarım – A.G., C.A.; Denetleme – A.G., G.K., H.A.; Veri Toplanması ve/veya İşlemesi – C.A., A.G.; Analiz ve/veya Yorum – A.G., G.K., H.A.; Literatür Taraması – C.A.; Yazıyı Yazan – C.A., A.G.; Eleştirel İnceleme – G.K., H.A.

Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

References

1. Compain C, Sacre K, Pue'chal X, Klein I, Vital-Durand D, Houeto JL, et al. Central nervous system involvement in Whipple disease: clinical study of 18 patients and long-term follow-up. Medicine (Baltimore) 2013; 92: 324-30. [CrossRef]
2. Pauletti C, Pujia F, Accorinti M, Pauri F, Tinelli E, Bianco F, et al. An atypical case of neuro-Whipple: Clinical presentation, magnetic resonance spectroscopy and follow-up. J Neurol Sci 2010; 297: 97-100. [CrossRef]
3. Rusina R, Keller O, Sima R, Zamecnik J. Peripheral neuropathy in Whipple's disease: a case report. Cesk Patol 2012; 48: 97-9.
4. Ojeda E, Cosme A, Lapaza J, Torrado J, Arruabarrena I, Alzate L. Whipple's disease in Spain: a clinical review of 91 patients diagnosed between 1947 and 2001. Rev Esp Enferm Dig 2010; 102: 108-23. [CrossRef]
5. Panegyres PK, Edis R, Beaman M, Fallon M. Primary Whipple's disease of the brain: characterization of the clinical syndrome and molecular diagnosis. QJM 2006; 99: 609-23. [CrossRef]
6. Hurth K, Tarawneh R, Ghoshal N, Benzinger TLS, Clifford DB, Geschwind M, et al. Whipple's Disease Masquerades as Dementia with Lewy Bodies. Alzheimer Dis Assoc Disord 2015; 29: 85-9. [CrossRef]
7. Benito-León J, Sedano LF, Louis ED. Isolated central nervous system Whipple's disease causing reversible frontotemporal-like dementia. Clin Neurol Neurosurg 2008; 110: 747-9. [CrossRef]

8. Christidi F, Kararizou E, Potagas C, Triantafyllou NI, Stamboulis E, Zalonis I. Neurocognitive impairment in Whipple disease with central nervous system involvement. Cogn Behav Neurol 2014; 27: 51-6. [CrossRef]
9. Tábuas-Pereira M, Vicente M, Coelho F, Santana I. Prosopagnosia as the Presenting Symptom of Whipple Disease. Cogn Behav Neurol 2016; 29: 100-6. [CrossRef]
10. Manzel K, Tranel D, Cooper G. Cognitive and behavioral abnormalities in a case of central nervous system Whipple disease. Arch Neurol 2000; 57: 399-403. [CrossRef]
11. Magherini A, Pentore R, Grandi M, Leone ME, Nichelli PF. Progressive supranuclear gaze palsy without parkinsonism: a case of neuro-Whipple. Parkinsonism Relat Disord 2007; 13: 449-52. [CrossRef]
12. Schröter A, Brinkhoff J, Günthner-Lengsfeld T, Suerbaum S, Reiners K, Messmann H, et al. Whipple's disease presenting as an isolated lesion of the cervical spinal cord. Eur J Neurol 2005; 12: 276-9. [CrossRef]