Syndrom of Headache Accompanied with Transient Neurologic Deficits and Cerebrospinal Fluid Lymphocytosis

Beyin Omurilik Sıvısı Lenfositozu ve Geçici Nörolojik Bulguların Eşlik Ettiği Baş Ağrısı Sendromu

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ABSTRACT

The syndrome of headache accompanied with transient neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL), is a rare, benign and self limiting syndrome. In the 2nd Edition of the International Classification of Headache Disorders, HaNDL syndrome was defined in secondary headache group as "Headache attributed to non-vascular intracranial disorder". The etiology of HaNDL is still unknown. In recent years, some authors have shown that ion channel autoimmunity might at least partially contribute to HaNDL pathogenesis. In this paper, the definition of HaNDL syndrome, clinical picture and epidemiology of HaNDL syndrome, etiopathogenesis, differential diagnosis and treatment will be reviewed with the recent literature. (*Archives of Neuropsychiatry 2013; 50 Supplement 1: S52-S55*)

Key words: Headache, transient neurologic deficits, cerebrospinal fluid lymphocytosis

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ÖZET

Beyin omurilik sıvısı (BOS) lenfositozu ve geçici nörolojik bulguların eşlik ettiği baş ağrısı ("headache accompanied with transient neurologic deficits and cerebrospinal fluid lymphocytosis"; HaNDL) sendromu; iyi gidişli, kendi kendini sınırlayan ve nadir görülen bir sendromdur. Uluslararası Baş Ağrısı Bozuklukları sınıflamasının ikinci baskısında HaNDL sendromu, sekonder baş ağrılarının içinde "damar dışı kafa içi hastalıklarıyla ilişkili baş ağrıları" olarak tanımlanmıştır. Etiyolojisi tam olarak bilinmese de son yıllarda, iyon kanalı otoimmünitesinin HaNDL patogeneze kısmen katkı sağlayabileceği bazı yazarlar tarafından gösterilmiştir. Bu yazıda, HaNDL sendromunun tanımı, klinik tablo ve epidemiyolojisi, etiopatogenezi, ayırıcı tanısı ve tedavisi son literatür eşliğinde gözden geçirilecektir. (*Nöropsikiyatri Arşivi 2013; 50 Özel Sayı 1: S52-S55*)

Anahtar kelimeler: Baş ağrısı, geçici nörolojik bulgular, beyin omurilik sıvısı lenfositozu

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Definition and History

"Headache accompanied with transient neurologic deficits and cerebrospinal fluid lymphocytosis"; (HaNDL) syndrome was named as "pseudomigraine accompanied by lymphocytic pleocytosis" previously. Bartleson et al. defined HaNDL syndrome in 1981 for the first time reporting 7 patients with migraine-like attacks in association with CSF lymphocytosis (1). In these patients, severe episodic headache was found before sensory, motor, speech and visual disorders. Berg and Williams reported 7 new patients in 1995 and proposed that this syndrome might be related with a unique response developing to a single virus or various viral agents (2). In 1997, Gómez-Aranda et al. also made a clinical definition by analysing 50 patients who had HaNDL syndrome (3).

In the classification published by the International Headache Association in 2004, HaNDL syndrome was defined in the last order among "headaches related with extravascular intracranial diseases" which is one of the subgroups of secondary headaches (group 7, code 7, 8) (4).

In this classification, the diagnostic criteria of HaNDL were defined as follows: A. Presence of moderate or severe headache episodes which last for hours; B. Neuroimaging with lymphocytic predominant CSF pleocytosis (>15 cells/microliter, normal CSF culture and normal etiological tests; C. Transient neurological findings accompanied by headache attacks or occurrence of these findings just after headache and a close temporal relation between onset of headache and development of CSF pleocytosis;

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D. Recurrence of headache and neurological finding episodes in approximately 3 months (4).

Clinical Picture and Epidemiology

HaNDL syndrome is observed more frequently in men aged between 15 and 40 years (68%) compared to women (5, 6). A history of migraine is present in approximately 26% of the patients (7). The typical clinical picture includes moderate or severe headache episodes with a number ranging between 1 and 12 accompanied by variable neurological finding episodes (6, 7). Headaches are unilateral or bilateral and predominately throbbing (6). Rarely, leukocytosis and fever may also accompany the picture (6, 7). The most common transient neurological findings include sensory disorder (78% of the episodes), aphasia (60%) and motor disorders (56%) (6, 7). Migraine-like visual symptoms may rarely be observed (%12) (6, 7). Sensory signs frequently start with numbness in the hand and progresses with a numbness pattern increased in the arm, face and tongue in order. The trunk and legs are rarely involved (3). In HaNDL syndrome, acute confusional picture characterized with episodic change in consciousness and agitation may rarely be observed. 5 patients presenting with acute confusional picture have been reported in the literature so far (8, 9, 10, 11). In 4 of these patients, agitation has been reported to accompany the clinical picture (9, 10, 11). In addition, long-term confusional picture resembling psychosis and requiring long-term hospitalization and agitation may also be observed in association with HaNDL syndrome (9, 11). Blurred vision, photophobia, homonymous hemianopsia, photopsia, cortical blindness, papilledema, increased intracranial pressure, 6th cranial nerve palsy and transient total external ophthalmoplegia may also rarely accompany HaNDL syndrome (12, 13).

In HaNDL syndrome, CSF lymphocytic pleocytosis (10-760/mm³) and increased CSF protein (96% of the cases) are observed. Oligoclonal band is found to be negative (6, 7). The patients do not show clinical symptoms between the episodes and after symptomatic periods. These episodes which generally end in weeks or months are separated with headache periods or asymptomatic periods during which neurological examinations are normal (3).

Cranial imaging tests are generally normal in HaNDL syndrome (5, 6, 7, 11). Although cranial diffusion-weighted magnetic resonance (MRI) tests are normal (14, 15, 16, 17), abnormalities have been reported on perfusion-weighted examinations in recent studies (14, 16, 17). In another study including one case, diffusion limitation was shown in the corpus callosum splenium region (18). In addition, rare small areas of high signal were reported on cranial MRI examination in some studies (19, 20). On single photon emission computerized tomography (SPECT) in HaNDL syndrome, findings compatible with transient focal cerebral hypoperfusion have been found in relation with the neurological findings during the acute phase (3, 8, 21). It has been reported that prominent VEP amplitude (22) or reduced VEP amplitude (23) may be found in addition to normal results (7) on VEP (visual evoked potential) examinations.

On electroencephalogram (EEG), focal, non-epileptic, intermittent slow waves with a character of theta or delta wave have been defined (10, 17, 23, 24).

Etiopathogenesis

Although the etiology of HaNDL which has a good prognosis and which is observed rarely is not clear (25), theories focused on parainfectious and autoimmune pathophysiology are still being debated (24, 26). In some studies, it has been proposed that the underlying cause may be inflammatory diseases of the central nervous system (CNS) (1, 3, 5, 24). It has been suggested that the antibodies produced by the immune system activated by way of viruses or autoimmune diseases may lead to CSF pleocytosis and aseptic inflammation which affects leptomeningeal structures resulting in neurological findings (7). Detailed screening tests performed for infectious agents are found to be negative in most patients with HaNDL, whereas cases with serological evidence of human herpes virus-6 infection have been reported (24). A CMV-related meningoencephalitis picture which showed similar clinical and laboratory properties as HaNDL syndrome and in which virus was isolated in CSF was reported in a previous study (5).

No mutation or polymorphism was detected in gene analysis studies of CACNA1A which is one of the subunits of the voltage-gated calcium channel performed in HaNDL syndrome which shows similar clinical properties as familial and sporadic hemiplegic migraine (27). Recurring and self-limiting transient neurological findings observed in HaNDL syndrome and CSF lymphocytosis are among the properties shared by autoimmune encephalitis related with ion channel antibodies (28). In another study published recently, high titers of antibody against CACNA1H protein which is one of the subunits of T-type calcium channel were found in 2 patients with HaNDL syndrome. This supported the view that ion channel autoimmunity may partially contribute to the pathogenesis of the syndrome (29).

Differential Diagnosis

The pictures which can be confused clinically with HaNDL syndrome include mainly migraine with aura or headache accompanied by recurrent aura and familial hemiplegic migraine in which reversible neurological findings and CSF lymphocytosis may be observed (27). HaNDL syndrome may be differentiated from this picture with absence of classical aura findings and familial history of hemiplegic migraine. Other significant pathologies including acute stroke, meningoencephalitis, meningitis, epilepsy, granulomatous and neoplastic arachnoiditis, neurobrucellosis, neurosyphilis, neuroborreliosis, mycoplasma infection, reversible posterior leukoencephalopathy syndrome, encephalitis, CNS vasculitis and reversible cerebral vasoconstriction should be differentiated from HaNDL syndrome both by clinical picture and investigations including serum autoantibodies, CSF examination and imaging (EEG, MRI etc.) (4, 7, 30).

Treatment

HaNDL syndrome which occurs as self-limiting episodes usually does not require treatment, since it has a good prognosis. However, systemic or oral corticosteroids (12, 17), beta receptor or calcium channel blockers (7, 17) and acetazolamide which is given for papilledema which is observed rarely (12) are among the treatment agents used in previous studies.

In addition, agents used in migraine prophylaxis including mainly antiepileptics may be used in preventing the attacks, since attacks similar to the clinical picture observed in migraine with aura are present in this syndrome. However, long-term controlled studies related with treatment of this syndrome which is observed rarely are absent in the literature except for individual case presentations.

In a case presentation published in recent years in which a patient with HaNDL syndrome was presented, 1000 mg/day valproic acid was used in treatment and a positive response was obtained (17). However, long-term controlled studies related with treatment of this syndrome which is observed rarely are absent in the literature except for individual case presentations. In addition, it is difficult to conclude if the responses observed depend on the drugs given or the disease's natural course because of the self-limiting property of this syndrome.

Conclusion

Since HaNDL syndrome is observed rarely, it may be overlooked or may be diagnosed falsely in clinical practice. In a patient who has headache accompanied by recurrent neurological disorder episodes, CSF pleocytosis and normal imaging tests, HaNDL syndrome should be absolutely considered. It is considerably important that this syndrome which has a good prognosis is defined and differentiated from pictures which need treatment in terms of avoiding unnecessary therapies including thrombolysis and long-term antimicrobial treatment.

Abbreviations

CSF: Cerebrospinal fluid; HaNDL: Headache accompanied with transient neurologic deficits and cerebrospinal fluid lymphocytosis; MRI: Magnetic resonance imaging; SPECT: Single photon emission computerized tomography; VEP: Visual evoked potential; EEG: Electroencephalography; CNS: Central nervous system

References

1. Bartleson JD, Swanson JW, Whisnant JP. A migrainous syndrome with cerebrospinal fluid pleocytosis. *Neurology* 1981; 31:1257-1262.
2. Berg MJ, Williams JS. The transient syndrome of headache with neurology deficits and CSF lymphocytosis. *Neurology* 1995; 45:1648-1654.
3. Gómez-Aranda F, Cañadillas F, Martí-Massó JF, Díez-Tejedor E, Serrano PJ, Leira R, Gracia M, Pascual J. Pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. A report of 50 cases. *Brain* 1997; 120:1105-1113.
4. Headache classification subcommittee of the International Headache Society. The international Classification of the headache disorders, 2nd ed. *Cephalalgia* 2004; 24(Suppl 1):1-160.
5. Chalupka Devetag F. Headache with temporary neurological symptoms and lymphocytic pleocytosis: a case report and etiologic hypothesis. *Neurol Sci* 2002; 23:123-125.
6. Pascual J, Valle N. Pseudomigraine with lymphocytic pleocytosis. *Curr Pain Headache Rep* 2003; 7:224-228.
7. Tsang BK, Kwong JC, Dewey HM. Case of syndrome of headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) with focal slowing on electroencephalogram. *Intern Med J* 2012; 42:944-947.
8. Ho BL, Lai CL, Hsu CY. Acute confusion in headache with neurologic deficits and cerebrospinal fluid lymphocytosis syndrome. *Am J Emerg Med* 2012; 30:2078.e7-8.
9. Mateo I, Pinedo A, Gómez-Beldarrain M, García-Moncó JC. Acute confusional state secondary to transient headache and neurological deficits with cerebrospinal fluid lymphocytosis. *Neurologia* 2004; 19:763-765.
10. Parissis D, Ioannidis P, Balamoutsos G, Karacostas D. Confusional State in the Syndrome of HaNDL. *Headache* 2011; 51:1285-1288.
11. Giorgetti A, Mariani G, Patruno GM, Romorini A. The transient syndrome of headache with neurological deficits, cerebrospinal fluid pleocytosis and acute confusional state: a case report. *J Headache Pain* 2005; 6:476.
12. Morrison DG, Phuah HK, Reddy AT, Dure LS, Kline LB. Ophthalmologic involvement in the syndrome of headache, neurologic deficits, and cerebrospinal fluid lymphocytosis. *Ophthalmology* 2003; 110:115-118.
13. Chan JW, Cheng C. Complete external ophthalmoplegia in headache, neurologic deficits, and cerebrospinal fluid lymphocytosis (HaNDL) syndrome. *Eye Lond* 2010; 24:198-199.
14. Segura T, Hernandez-Fernandez F, Sanchez-Ayaso P, Lozano E, Abad L. Usefulness of multimodal MR imaging in the differential diagnosis of HaNDL and acute ischemic stroke. *BMC Neurol* 2010; 10:120.
15. Gekeler F, Holtmannspotter M, Straube A, Klopstock T. Diffusion-weighted magnetic resonance imaging during the aura of pseudomigraine with temporary neurologic symptoms and lymphocytic pleocytosis. *Headache* 2002; 42:294-296.
16. Vallet AE, Desestret V, Tahon F, Cho TH, Nighoghossian N. Acute perfusion MR imaging in a HaNDL-like syndrome. *Cerebrovasc Dis* 2010; 29:98-100.
17. Yilmaz A, Kaleagasi H, Dogu O, Kara E, Ozge A. Abnormal MRI in a patient with headache with neurological deficits and CSF lymphocytosis (HaNDL). *Cephalalgia* 2009; 30:615-619.
18. Raets I. Diffusion restriction in the splenium of the corpus callosum in a patient with the syndrome of transient headache with neurological deficits and CSF lymphocytosis (HaNDL): a challenge to the diagnostic criteria? *Acta Neurol Belg* 2012; 112:67-69.
19. Berg MJ, Williams LS. The transient syndrome of headache with this syndrome, even though it still appears reasonable to neurologic deficits and CSF lymphocytosis. *Neurology* 1995; 45:1648-1654.
20. Walter CT, Grogan WA. Migraine with tardy pleocytosis. *Neurology* 1986; 36:733.
21. Fuentes B, Díez Tejedor E, Frank A. Syndrome of headache with neurological deficits and CSF lymphocytosis: a spreading depression mechanism? The role of SPECT. *Headache* 1998; 38:324-324.
22. Anagnostou E, Spengos K, Naoumis D, Paraskevas GP, Vassilopoulou S, Zis V, Vassilopoulos D. Lack of visual evoked potential habituation in the syndrome of HaNDL. *J Neurol* 2009; 256:1374-1376.
23. Fumal A, Vandenheede M, Coppola G, Di Clemente L, Jacquart J, Gérard P, de Noordhout AM, Schoenen J. The syndrome of transient headache with neurological deficits and CSF lymphocytosis (HaNDL): electrophysiological findings suggesting a migrainous pathophysiology. *Cephalalgia* 2005; 25:754-758.
24. Emond H, Schnorf H, Poloni C, Vulliamoz S, Lalive PH. Syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL) associated with recent human herpesvirus-6 infection. *Cephalalgia* 2009; 29:487-491.

25. Nakashima K. Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis: HaNDL. Intern Med 2005; 44:690-691.
26. Kürtüncü M, Tüzün E, Kaya D, İçöz S, Barış Baslo M, Ertaş M, Akman-Demir G, Eraksoy M. Anti-neuronal antibodies associated with headache with neurological deficits and cerebrospinal fluid lymphocytosis. J Headache Pain 2008; 9:333-335.
27. Chapman KM, Szczygielski BI, Toth C, Woolfenden A, Robinson G, Snutch TP, Spacey SD. Pseudomigraine with lymphocytic pleocytosis: a calcium channelopathy? Clinical description of 10 cases and genetic analysis of the familial hemiplegic migraine gene CACNA1A. Headache 2003; 43:892-895.
28. Vincent A, Bien CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: New developments and future challenges. Lancet Neurol 2011; 10:759-772.
29. Kürtüncü M, Kaya D, Zuliani L, Erdağ E, İçöz S, Uğurel E, Cavuş F, Aysit N, Birişik O, Vincent A, Eraksoy M, Vural B, Akman-Demir G, Tüzün E. CACNA1H antibodies associated with headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL). Cephalalgia 2013; 33:123-129.
30. Tan LH, Flower O. Reversible Cerebral Vasoconstriction Syndrome: An Important Cause of Acute Severe Headache. Emergency Medicine International Emerg Med Int. 2012; 303:152.