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Case Report

HaNDL Syndrome Presenting During Pregnancy: A Case Report and Review of the Literature

Gebelik Sırasında Oluşan HaNDL Sendromu: Olgu Sunumu ve Literatürün Gözden Geçirilmesi

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Summary

Headache associated with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) is a self-limiting syndrome characterized by sudden-onset headache with a temporary neurological deficit and cerebrospinal fluid (CSF) lymphocytosis. We aimed to disscus a case of HaNDL syndrome presenting during pregnancy with relevant literature. A 20-year-old female presented with a 5-day history of severe, bilateral throbbing headache accompanied by nausea, vomiting, and phonophobia. Approximately 2 days after the pain developed, she became acutely confused for less than 90 minutes. Two days after this episode, she experienced another confusional state and left hemiparesis. There were no symptoms consistent with meningoencephalitis. She was in her 11th week of pregnancy. A neurologic examination showed confusion, bilateral papilledema, and mild left hemiparesis. The neuroradiological examination was normal. The cerebrospinal fluid revealed lymphocytic pleocytosis, mildly elevated protein, and increased opening pressure. She recovered completely after 8 days. The precise etiology of HaNDL is unknown, although an inflammatory or infectious origin and autoimmune factors have been proposed. Moreover, the risk factors and medical conditions associated with HaNDL are also unknown. It is difficult to determine whether the pregnancy was coincidental or associated in this case. We believe that comprehensive studies are needed to clarify the risk factors and medical conditions associated with HaNDL. (Turkish Journal of Neurology 2014; 20:91-94)

Key Words: HaNDL syndrome, pregnancy, confusion, bilateral papilledema

Özet

Headache associated with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL) sendromu ani başlangıçlı baş ağrısı, geçici nörolojik defisit, beyin omurilik sıvısında (BOS) lenfositoz ile karakterize kendini sınırlayan bir sendromdur. Bu sunumda, gebelik sırasında HaNDL sendromu oluşan bir olguyu literatür eşliğinde tartışmayı amaçladık. Yirmi yaşında kadın hasta, 5 gün önce başın arkasından başlayıp tümüne iki yanlı yayılan, şiddetli, zonklayıcı baş ağrısı yaşamaya başlamıştı. Ağrıya bulantı, kusma ve fonofobi eşlik etmişti. Ağrı başladıktan 2 gün sonra, 1,5 saat içinde tamamen düzelen akut konfüzyonel tablodan geçmişti. Bu ataktan 2 gün sonra konfüzyonel durum tekrar etmiş ve tabloya sol hemiparezi eklenmişti. Meningoensefaliti düşündürecek bulgular yoktu. Hasta 11 haftalık gebeydi. Nörolojik muayenede hasta konfüzeydi. İki yanlı papil ödem ve hafif sol hemiparezisi mevcuttu. Nöroradyolojik incelemeleri normaldi. Hastaya lomber ponksiyon (LP) yapıldı. Açılış basıncı yüksek, protein düzeyi hafif yüksek, glikoz düzeyi eş zamanlı kan şekeriyle orantılıydı. Mikroskopik hücre bakısında lenfositik pleositoz olduğu saptandı. Hastanın klinik bulguları 8. günde tam olarak düzelmişti. Enflamatuar, enfeksiyoz ve otoimmün faktörlerin rolü olabileceği ileri sürülmüş olsa da HaNDL sendromunun etiyolojisi net olarak bilinmemektedir. Ayrıca, bu sendromla ilişkili olabilecek risk faktörleri ve medikal durumlar da bilinmemektedir. Bu olguda, HaNDL sendromunun gebelikle ilişkili veya tesadüfi bir birliktelik gösterdiğini ayırt etmek oldukça zordur. Bu sendromla ilişkili risk faktörleri ve medikal durumların tanımlanması için geniş çalışmalara ihtiyaç olduğunu düşünmekteyiz. (Türk Nöroloji Dergisi 2014; 20:91-94)

Anahtar Kelimeler: HaNDL sendromu, gebelik, konfüzyonel durum, iki yanlı papilödem

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Introduction

First described in 1981 by Bartleson using 7 cases, the syndrome was at first described in different ways such as migraine with cerebrospinal pleocytosis or lymphocytic pseudomigraine with pleocytosis (1,2,3).

Adding 7 new cases to the already published cases between 1974 and 1995 (33 in total), Berg et al. reviewed their clinical/laboratory findings and coined the name 'HaNDL' from the first letters of 'Headache with Neurologic Deficits and cerebrospinal fluid Lymphocytosis' and determined its diagnostic criteria (1).

The diagnostic criteria for HaNDL syndrome, which is the seventh group called 'headache attributed to non-vascular intracranial disorder' under secondary headaches (code 7.3.5) has been identified as below (4):

A. Episodes of migraine-like headache fulfilling criteria B and C

B. Both of the following

a. Accompanied or shortly preceded by the onset of at least one of the following transient neurological deficits lasting >4 hours: hemiparaesthesia, dysphasia, hemiparesis.

b. Lymphocytic pleocytosis (>15 white cells per µl) in otherwise etiologically normal cerebrospinal fluid (CSF).

C. One or both of the following;

a. Headache and transient neurological deficits have developed or significantly worsened in temporal relation to the CSF lymphocytic pleocytosis, or led to its discovery

b. headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF lymphocytic pleocytosis

D. Not better accounted for by another diagnosis.

In this paper, the case of a pregnant woman who was thought to be HaNDL is discussed with references to the literature.

Case

Twenty year old female patient came to our clinic with headache complaints. Her anamnesis suggested that she previously did not have headaches until 5 days ago when a severe, throbbing headache started spreading from the back of her head towards the front parts. The headache was accompanied by nausea, vomiting and phonophobia.

Two days after the onset of the pain, the patient went through an episode where she could not remember her location, people or names; could not find appropriate answers to questions and wandered aimlessly around the house for 1.5 hours. During this period, her word production was intact and she did not slur words.

Two days after this attack, she started having similar symptoms but she also had weakness on her left arm and leg. It was reported that the limb weakness went away spontaneously in 7-8 hours but her place-person disorientation remained. She did not have a history of infection in the past month. She did not have fever. She was 11 months pregnant.

Her place and person orientation was impaired during the neurological orientation but her time orientation was intact. She had bilateral papillary edema and mild left hemiparesis.

Biochemistry, hemogram, thyroid tests, sedimentation value, and the comprehensive autoanbody panel for vasculitic-rheumatological disorders were all normal. Cranial MR, venogram and electroencephalogram (EEG) did not show any pathological findings.

The opening pressure of lumbar puncture (LP) was 320 mm H_2O, protein level was 57 mg/dl and the glucose level was normal with relation to simultaneous blood sugar. The microscopic examination showed 110 leucocyte/mm3 with 90% of them being lymphocytes. There were no atypical-malignant cells indicating leptomeningeal involvement in her CSF. All bacteriological, fungal and viral microbiological tests for CSF and/or blood were negative.

The patient was started on paracetamol in the first day of admission. Acute confusional state and left hemiparesis recovered completely within the 6th hour of admission (14 hours in total). Her headache completely disappeared on the 8th day, and the papillary edema subsided noticeably on both eyes. The opening pressure of the control LP was 300 mmH_2O with 50 mg/dL protein, and it did not have any cells.

Discussion

These medical history, and clinical and laboratory findings pointed to HaNDL syndrome in the patient. The real prevalence of the syndrome is currently unknown. It affects both genders and does not show a meaningful gender dominance (1,3).

The majority of the patients describe a throbbing (81%) or pressing (12%) type of headache at an intensity they have not experienced before (1,3). The localization of the headache can generally be bilateral and less frequently unilateral. The duration of the headache is also variable, ranging from one hour to a week (19 hours in average). Nausea, vomiting, photophobia and phonophobia can accompany the headache (1,3). In addition, there were also reports of cases with mild or no headaches (3,5,6).

Neurologically, the most common symptoms are aphasia, hemiparesis and sensory symptoms (1,3). There were neurological deficits that were confined to one hemisphere in 80%, to basilar artery supply areas in 6% and to other brain areas in 14% of the cases. Seventy four percent of the temporary neurological deficits involved the left hemisphere. Pure motor aphasia (36%) was the most commonly seen speech disorder, followed by global aphasia (22%) and pure sensory aphasia (2%).

The patients rarely show confused state, papillary edema, 6th nerve paralysis and epileptic seizures. These patients do no show meningeal irritation findings (1,3,7-10). In single-case studies, visual symptoms such as bilateral blurry vision, homonym hemianopsia, nystagmus, photopsia and external ophthalmoplegia were also seen during the attacks (10-12). These neurological deficits can last from 5 minutes to a week (5 hours in average) (1,3). The attack count changes between 1 and 12. The longest attacks last for 12 weeks (1).

Another diagnostic criterion for HaNDL is the presence of lymphocytic pleocytosis (>15 cell/µl) in otherwise normal CSF (3,4).

The meaning and the cause of the lymphocytic pleocytosis in the CSF is unknown (3). In all of the patients, increased number of white blood cells (lymphocytic dominance up to 90%), 10-760 cell/ mm3), high CSF opening pressure (up to 400 mmH2O) in 55-73% of the patients, protein increase in 91-96% (up to 250 mg/dl) can be detected. Despite the complete clinical recovery, lymphocytosis in CSF may remain persevere (13).

Cranial MR and CT were found to be normal with the exception of a few cases and there were no syndrome-specific markers identified in those modalities (1,3).

There were a few hyperintensities in the T2 MRI of two patients and leptomeningeal contrasting in the cranial MRI of one patient who had Herpes 6 virus IgM antibodies detected in the serum (1,14).

In all case studies, the diffusion-weighted sequences of the cranial MRI was reported to be normal. In only one case there was diffusion restriction on the splenium of corpus callosum, which was previously reported to be due to meningoencephalitis (15). In another case, hypoperfusion in the right parieto-occipital region in the perfusion-weighted images, and right-dominant bilateral temporal and parietal sulcal deepening and swollen gray matter in FLAIR images were detected. These findings disappeared after the offset of the attack (16).

Cerebral angiography studies on the patients were found to be normal. Cerebral angiography is known to worsen the neurological deficit (1,17).

Pathological EEG findings were seen in 72% of the patients. Generally, the region that the neurological deficit is originating from shows focal generalized baseline sluggishness. In all patients, EEG goes back to normal following the disappearance of other symptoms (1,3,18,19).

SPECT studies show that the source of the neurological deficit has decreased blood flow, which recovers after the attack (20). In one patient, SPECT study conducted during a non-attack period showed reduced bilateral temporo-occipital blood flow. Researchers interpreted this as 'propagating cortical depression' triggered by meningeal inflammation, much like in migraine auras (21).

The pathogenesis of the disease is still unknown. In the early years, it was thought that the condition is nothing more than migraine and that the pleocytosis in CSF is the non-infectious central nervous system inflammation secondary to migraine (1,3).

Some researchers, on the other hand, argued that the condition arises due to a viral infection and that virus plays a role in the pathogenesis either directly or via immune-mediated mechanisms with post-infectious molecular similarity (1,3,9,19).

To this day, however, there has not been a single, isolated virus that could be hold responsible for the etiology of the disease except for a small number of case studies (1,3). Single-case studies with Herpes 1, 2 and 6 and cytomegalovirus, borrelia burgdorferi, echovirus 30 and Epstein-Barr virus were reported (1,3,14,22).

In more recent studies, new anti-neuronal antibodies directly against cerebral and cerebellar Purkinje cells differently, as opposed to the classical anti-neuronal antibodies (anti-Hu, anti-Ri, anti-nuclear antibodies) were identified in 2 cases and this motivated the hypothesis that there could be an immune response to the neurons and that abnormal humeral immunity could play a role in the pathogenesis (23).

In addition, when the recurring but self-restricting nature of the neurological deficit and CSF lymphocytosis is taken into consideration, the disorder can be thought of an autoimmune encephalitis related to antibodies against ion channels. In a study that investigated this hypothesis, the finding that 2 out of 4 cases showed CACNA1H (T-type voltage-gated calcium channels formed against alpha 1H subunit) antibodies suggested that ion channel antibodies and therefore autoimmune mechanisms may play a role in the pathogenesis of the syndrome (24).

We chose to present this case due to two reasons. First, even though the patient manifested the classical clinical/laboratory properties of the syndrome, her neurological symptoms included the confused state and papillary edema which are rarely seen together in the frequent presentations of HaNDL syndrome.

Second, the patient was pregnant. Except for 6 patients, the fact that no additional risk factor or co-occurring condition was identified for over 100 patients in HaNDL literature is interesting. When these 6 cases were investigated more carefully, each one of them had one of the following conditions: hyperthyroid, diabetes mellitus and dyslipidemia, hypertension, alcohol use, oral contraceptive use, hypertension, dyslipidemia and sleep apnea (9,12,20,25,26). Pregnancy has a special place in the neurology practice. It is very difficult to answer the question of whether the pregnancy played a role in the syndrome pathogenesis or whether it was coincidental in the present case. Since the pregnancy is a risk factor for the emergence of certain neurological disorders and that the course of certain disorders can be altered during pregnancy, it is possible to think that pregnancy may also constitute a risk factor for HaNDL syndrome. The changes in estradiol (E2), estriol (E3), progesterone, corticosteroid and prolactin levels during pregnancy causes changes in the immune response (27).

While the changing ratios of estrogen and progesterone reduce inflammatory macrophages of natural killer cell activity, Th1 cells and inflammatory cytokines, the anti-inflammatory cytokine ratios increase. These changes in the immune system may exert an effect on the course of autoimmune and infectious diseases during pregnancy (27). We think there is need for extensive research to identify the risk factors directly or indirectly affecting the pathogenesis of this syndrome and/or medical conditions associated with it.

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