A Syndrome of Headache and Neurological Deficits with Cerebrospinal Fluid (CSF) Lymphocytic Pleocytosis (Handl) with Diffuse Vasogenic Leakage of Gadolinium MRI Contrast into the Extra-Axial CSF Cisterns

Neema Patel1*, Vivek Gupta1, Kevin Barrett2, and Prasanna Vibhute1

1Department of Radiology, Mayo Clinic, USA
2Department of Neurology, Mayo Clinic, USA

ABSTRACT

We present a unique imaging presentation of Headache and Neurological Deficits with Lymphocytic pleocytosis (HaNDL) Syndrome.

ABBREVIATIONS

HaNDL: transient Headache and Neurologic Deficits with cerebrospinal fluid Lymphocytosis; ICHD-III: International Classification of Headache Disorders-3rd edition; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; CT: Computerized Tomography

INTRODUCTION

A syndrome of migraine-like headaches accompanied or preceded by transient neurological deficits lasting for greater than 4 hours with cerebrospinal fluid lymphocytic pleocytosis (HaNDL) is classified in the International Classification of Headache Disorders (ICHD-III) as headache attributed to non-vascular intracranial disorder [1]. One of the ICHD-III diagnostic criteria for HaNDL syndrome is normal neuroimaging outside of the episode. The full spectrum of neuroimaging abnormalities during the acute episode may show delayed brain perfusion without diffusion-weighted imaging abnormalities, and narrowing of cerebral arteries [1]. We found a single case report of this syndrome describing grey matter edema, sulcal enhancement and cerebral perfusion abnormalities during the acute episode [1]. Although other reports of imaging findings in HaNDL exist in the literature, most of these reports either mention a positive association with an etiologic agent or lack mention of workup to exclude a potential etiologic association [3-11]. We report a MRI finding of diffuse leptomeningeal vasogenic leakage of intravenous gadolinium into the extra-axial cerebrospinal fluid (CSF) during the acute episode of HaNDL in a 35 year old man without past history of headaches with a presentation of migraine-like headaches with transient neurologic deficits that lasted for 3 weeks and CSF lymphocytic pleocytosis. We believe this finding may have implications upon understanding of the pathophysiology underlying this disorder. To our knowledge, this is the first case report in English language medical literature which clearly illustrates CSF leakage of gadolinium in HaNDL.

CASE PRESENTATION

A 35-year-old male patient presented to the emergency room as stroke alert with acute onset of right sided weakness followed by severe headache. The episode began with paresthesia in his right arm marching proximally and subsequently spreading to the right hemi body and leg. The symptoms progressed to right-sided hemiparesis and blurred vision with peripheral field defects. An emergent Computed Tomography (CT) scan of the head was normal. The neurological deficits rapidly resolved followed by
worsening headache. Upon admission, a more detailed history revealed that he had experienced 6 similar stereotypical neurological episodes over 3 weeks prior to this presentation. Occasionally, the left side was also affected, although to a lesser degree. In each episode, the prodrome of deficits lasted 30-60 minutes, followed by a debilitating headache, photophobia, and fatigue, which usually resolved overnight. There were no triggers or medication associated with these episodes. The patient’s past, social, and family histories were noncontributory. The MRI obtained upon admission showed striking hyperintensity of the entire extra-axial CSF on 5 minute post IV gadolinium FLAIR images (Figure 1 A-B) and diffuse abnormal leptomeningeal enhancement on enhanced T1-weighted sequence (Figure 1 C). This FLAIR appearance was suspected to be due to vasogenic leakage of gadolinium from the leptomeninges. This leakage of gadolinium was unequivocally verified on a 4-hour delayed T1 weighted MRI (Figure 1 D). His vital signs, neurological exam, and EEG were normal during the hospital stay. Lumbar puncture showed a normal opening pressure (15 cm of water), normal glucose (57 mg/dL), elevated proteins (245 mg/dL) and lymphocytic pleocytosis (162 WBC/mL, 97% lymphocytes and 3% mononuclear cells). Extensive CSF analysis including serology was negative for syphilis, Histoplasma, Brucella, Human Immunodeficiency Virus (HIV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Ebstein Barr Virus (EBV), West Nile Virus (WNV), Cytomegalovirus (CMV), JC virus, and paraneoplastic antibodies. CSF bacteriology, AFB, and fungal cultures were also negative. Thyroid function tests were also normal. His headache resolved 24 hours following admission. Although the duration of transient neurological deficits lasted for less than 4 hours, a final diagnosis of HaNDL was made as extensive workup failed to establish other etiologies. A repeat MRI and CSF analysis were obtained prior to discharge five days after admission. The MRI revealed resolution of the previously seen diffuse leptomeningeal enhancement and abnormal CSF FLAIR signal (Figure 2). There was also decreased CSF lymphocytic pleocytosis (125 WBC/mL with 87 % lymphocytes, 12% mononuclear cells, and 1% eosinophils) and protein (146 mg/dL). Immunocytochemistry showed a predominance of small T lymphocytes (CD3+) and only rare B lymphocytes (CD20+).

**DISCUSSION**

The International Classification of Headache Disorders, 3rd Edition (ICHD-III, 7.3.5) classifies HaNDL as migraine-like episodes with neurological deficits including hemiparesthesias, hemiparesis, and/or dysphasia and uncommonly visual symptoms lasting several hours with lymphocytic pleocytosis which resolves spontaneously within 3 months [1]. Furthermore, HaNDL is attributed to a non-vascular intracranial disorder with normal interictal neuroimaging [1]. This rare condition has been labeled in the past as "a migrainous syndrome with cerebrospinal fluid pleocytosis," "pseudomigraine with lymphocytic pleocytosis" or "pseudomigraine with temporary neurologic symptoms and lymphocytic pleocytosis" [1]. HaNDL is a self-limiting syndrome occurring in young and middle-age adults, typically men, characterized by one or more episodes of severe headache, transient neurologic deficits and CSF lymphocytic pleocytosis. On the contrary, migraine headaches are more common in women and typically present as chronic unilateral headaches with normal CSF. The headaches in HaNDL are severe and last several hours per the ICHD-III criteria. Furthermore, these headaches could precede, coincide, or follow the episodes of transient neurological deficits. As exemplified by our patient, the sensory
symptoms are the most common, followed by aphasia and motor deficits. The patient also showed a ‘march’ of symptoms from the right upper extremity, to body, and to his lower extremity, which is occasionally seen in HaNDL, but more commonly reported in migraine aura. The CSF lymphocytosis and increased protein occur in more than 90% of patients, while the opening pressure is elevated in greater than 50% of patients with HaNDL [1]. With the exception of somewhat short lasting deficits (30-60 minutes rather than several hours per ICHD-III criteria), the entire clinical presentation, presence of CSF lymphocytosis, and extensive negative testing for infectious and other etiologies (including tests for syphilis, WNV, HIV, Histoplasma, Brucella, Cryptococcus, VZV, EBV, CMV, JC Virus, HSV as well as drugs of abuse) support the most likely diagnosis of HaNDL for this patient. There are very few reports of HaNDL and cases mimicking HaNDL due to other etiologies and furthermore very few cases describing leptomeningeal enhancement on MRI [2-11]. One report showed localized subtle sulcal enhancement on FLAIR. The MRI of our patient during the acute episode not only showed leptomeningeal enhancement on post gadolinium T1 weighted images, but also diffuse hyperintensity of the subarachnoid spaces bilaterally over the entire hemispheres on FLAIR, indicating rapid gadolinium leakage (within 5 minutes) due to disruption of blood-brain barrier and markedly increased permeability of leptomeningeal vessels. The rapidity of leakage strongly suggests a vasogenic mechanism. Absence of parenchymal, dural, and ventricular CSF enhancement weighs against these sources of leakage. The exact underlying mechanism is open to speculation. One potential mechanism could be T-lymphocyte cytokine mediated increase in vascular permeability. This is the first report convincingly demonstrating vasogenic leakage of gadolinium into CSF in HaNDL syndrome after excluding other etiologies. The significance of this observation is several-fold. Our case suggests that increased leptomeningeal vascular permeability may be a component of HaNDL pathophysiology. Vasogenic contrast leakage into CSF has been reported in headaches with neurological deficits, including hemiplegic migraine [3,4]. Thus, the pathophysiology of HaNDL might overlap with migraine. Contrast-enhanced FLAIR, therefore, should be considered in the MRI protocol of acute headaches with neurological deficits, as it is more sensitive in detecting leptomeningeal enhancement and contrast leakage into CSF. Future use of contrast-enhanced FLAIR may further support our observations.

CONCLUSION

Leptomeningeal vasogenic leakage of gadolinium is a neuroimaging finding in acute phase of HaNDL. We recommend contrast-enhanced FLAIR sequence, in addition to T1 MRL, to improve detection of leptomeningeal vasogenic leakage.

REFERENCES


