

CASE REPORT

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An adult woman with transient headache, neurological deficits, and lymphocytic pleocytosis (HaNDL syndrome) with intracerebral melanosis: case report

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Abstract

Headache with a neurological deficit and cerebrospinal fluid (CSF) lymphocytosis (HaNDL) is usually under-recognized and under-reported. HaNDL is a self-limiting condition, but the grave symptoms require a large-scale differential diagnosis. We report a case of a 24-year-old female who developed dysarthria for several hours and decreased use of the right arm with right-sided facial weakness. After extensive investigation of blood, CSF, and neuroimaging, we excluded central nervous system infections and autoimmune and vascular diseases. A diagnosis of HaNDL was made according to clinical symptoms and CSF analysis. The prognosis was good, and the symptoms resolved. Repeated physical examination after 48 h was unremarkable. HaNDL is probably not as rare as commonly thought; awareness of its existence can avoid unnecessary and potentially harmful investigations and therapies. The clinical challenge relies on the fact that it remains a diagnosis of exclusion.

Introduction

The syndrome of transient headache and neurologic deficits with cerebrospinal fluid (CSF) and lymphocytosis (HaNDL) was first described in 1981 and was known as pseudomigraine with CSF pleocytosis [1]. It is a benign self-limited condition characterized by one or more episodes of severe headache, transient neurologic deficits, and CSF lymphocytic pleocytosis. The most frequent neurologic signs are hemiparesis, hemisensory disturbances, and aphasia. The mean number of episodes for each patient is three, with a maximum of twelve. However, single episodes occur in approximately one fifth of patients [2]. HaNDL is included in the second edition of the International Classification of Headache Disorders [3] and is classified as a “headache attributed to nonvascular intracranial disorder.” The distinguishing feature of HaNDL is CSF pleocytosis, as seen in a series of adult patients with HaNDL who had typical lymphocytic

predominance and elevated opening pressure, ranging from 10 to 40 cm (mean 23 cm) [4].

HaNDL is not rare as commonly thought. Awareness of its existence can avoid unnecessary and potentially harmful investigations and therapies.

Case presentation

A 28-year-old female developed dysarthria for several hours and decreased use of the right arm with right-sided facial weakness. Past medical history was significant for attacks of throbbing headaches that last for 4–16 h and occur 3 to 4 times a month. The attacks were associated with photophobia, phonophobia, and vomiting. Two months ago, one of these headache episodes was accompanied by transient neurologic deficits. There was no history of illicit drug use or recent foreign travel. Family history was irrelevant. On admission, her vitals were normal, and she was alert and fully orientated. She had a headache, mild photophobia, and right arm weakness graded as 4/5 using the Medical Research Council (MRC) grading system.

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Neck stiffness and fever were absent. Physical examination after 48 h was unremarkable.

Laboratory evaluation included a white blood cell (WBC) count of $4.73/\text{mm}^3$ with 62.4% neutrophils, 28.1% lymphocytes, 7% monocytes, and 4% eosinophils. High sensitive C-reactive protein was 1.63 (less than 5 mg/L). Rheumatoid factor and antinuclear antibody were negative. Comprehensive metabolic panel (liver function tests, renal function tests, electrolytes, ketones, glycosylated HB, thyroid, and parathyroid function) was within normal limits.

Cerebrospinal fluid studies obtained under sedation revealed $191 \text{ WBC}/\text{mm}^3$ with 98% lymphocytes and 2% monocytes, glucose 58 mg/dL, protein 40 mg/dL, and opening pressure 38 cm. CSF polymerase chain reaction (PCR) assays for herpes simplex virus (HSV), enterovirus, and *Mycobacterium tuberculosis* were negative. Tuberculin skin testing, Zeil Nilson, and culture for acid-fast bacilli (AFB) were negative. Human immunodeficiency virus, Epstein-Barr virus, *Brucella*, Lyme, and *Bartonella* serologies were negative as well. EEG was done and showed no abnormality.

Imaging included a non-contrast computed tomographic (CT) scan of the brain which showed bilateral medial cerebellar symmetrical hyperdense areas. Magnetic resonance imaging (MRI) was done and demonstrated increased signal at both cerebellar lobes with involvement of dentate nucleus in both sides; the lesions show a blooming effect of melanin at GRE sequence. The lesions are hypodense at T2WI with no evidence of enhancement after IV contrast administration (non-specific finding). The lesion shows no mass effect and is not surrounded with edema (Fig. 1).

Discussion

In this case of a young female presenting with headache and transient neurologic deficits with cerebrospinal fluid

(CSF) lymphocytosis, we attempted to exclude other possible underlying etiologies. Although HaNDL is a self-limiting condition, it is part of a large differential diagnosis. Complicated or hemiplegic migraine, aseptic meningitis, meningoencephalitis, and stroke are among many conditions that could mimic this syndrome. Exclusion of infectious causes and acute cerebrovascular insult such as ischemic stroke is essential for diagnosing HaNDL syndrome. Stroke in young remains a very important condition that must be excluded because of the limited time window for thrombolysis. Diffusion-weighted MRI is highly accurate in acute ischemic stroke of less than 6 h duration and recommended when differentiating stroke from HaNDL [5].

Hemiplegic migraine is clearly different from HaNDL. Hemiplegic migraine starts before the patient is 20 years old and is often associated with a family history of hemiplegic migraine or migraine. A constant feature of HaNDL is the CSF lymphocytic pleocytosis. CSF pleocytosis of more than 10 to 15 mononuclear cells/ mm^3 does not occur in migraine [6]. Interestingly, unlike migraine, HaNDL has a slight predilection for males [7]. Moreover, most patients do not have a previous history of migrainous headaches. HaNDL also is separated easily from the autosomal dominant syndrome of recurrent migraine coma with focal cerebral oedema, CSF pleocytosis, and progressive cerebellar ataxia [8].

Despite thorough evaluation for infectious etiologies of HaNDL in both children and adults, its possible infectious origin has not been yet identified [9]. However, there are reports of cases whose CSF analysis showed a positive PCR for human herpesvirus type 7 (HHV-7) [10] and human herpesvirus-6 infection [11]. This suggests a possible role of a viral infection in the etiology of HaNDL which is mostly immune related. There are many infectious conditions that can present with

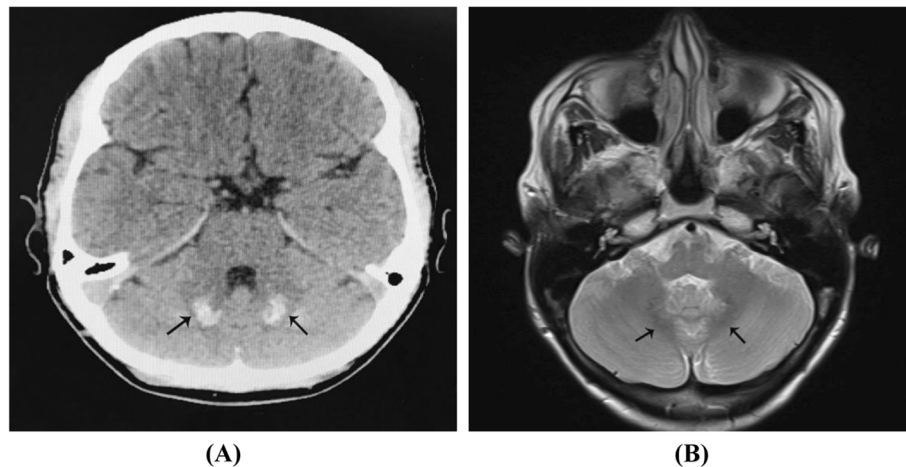


Fig. 1 Computed tomography (CT) scan (a) and magnetic resonance imaging (MRI) (b) abnormalities

neurological deficits, headache, and CSF pleocytosis, but the transient nature of the deficits and lack of consistently discoverable etiology despite extensive evaluations typify HaNDL. Recurrent pleocytosis raises the diagnostic possibility of HSV (Mollaret's) meningitis, which presents with episodic mild fever, photophobia, headache, and change in mental status [12]. Characteristic CSF findings include marked pleocytosis with neutrophils, lymphocytes, and large mononuclear (Mollaret) cells that are typical for this disease, but not for HaNDL.

It was proposed that HaNDL could be an autoimmune disorder, conceptually similar to Guillain-Barré syndrome [7]. Approximately one third of patients with HaNDL have symptoms of a "viral" illness in the preceding 3 weeks. It is possible that such an infection could activate the immune system, which would produce antibodies to neuronal or cranial vessel antigens. This may induce the transient neurologic symptoms throughout a spreading depression-like mechanism and then aseptic vasculitis, which would account for the "vascular" headache and CSF pleocytosis [1].

Conventional brain MRI, as a rule, is normal, and in fact, Gómez-Aranda et al. [7] assume this as a diagnostic criterion. However, there were reports of abnormal findings mostly non-specific in many cases [13, 14] like in our case. In the present case, melanin deposits were detected in the cerebellum with the involvement of dentate nucleus in both sides without any associated cutaneous lesions and the case fulfilled the criteria of HaNDL, so we considered this finding as just non-specific association. Cerebral angiography has been almost invariably normal in cases with HaNDL [7] and can be responsible for triggering an episode of neurologic deficit as reported by Cifelli and Vaithianathar [15].

Conclusion

HaNDL is probably not as rare as commonly thought; it is under-recognized and under-reported and remains a diagnosis of exclusion. Awareness of its existence can avoid unnecessary and potentially harmful investigations and therapies. The prognosis is benign, and the treatment is symptomatic.

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Authors' contributions

All authors participated in the design of the study, collection and review of clinical data, and drafting and writing of the manuscript of the study. All authors read and approved the final manuscript.

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Availability of data and materials

The data results generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate

A written informed consent was obtained from every patient or his/her relative to be included in the study. This study was approved by the local research board of the Neurology Department, Faculty of Medicine, Zagazig University, Egypt.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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