CASE REPORT

HaNDL syndrome in a 14-year-old girl

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SUMMARY

Transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL syndrome) consists of recurrent headaches with focal neurological signs, which can include motor, sensory and aphasic symptoms. Although considered rare, it is becoming increasingly recognised in clinical practice due to the accumulation of case reports. The pathophysiology remains unclear although changes in the neurovascular resemble those found in migraine, which are thought to be triggered by an infectious process. HaNDL can mimic various serious, including life-threatening, diseases, such as stroke and meningoencephalitis, which is why vigorous tests should be sought before this diagnosis of exclusion can be reached. Treatment is symptomatic and the prognosis is excellent. A literature review of the topic is discussed. We report an adolescent girl who presented with recurrent expressive dysphasia and right-sided hypoaesthesia and moderate occipital headaches who was diagnosed with HaNDL syndrome.

BACKGROUND

Transient headache and neurological deficits with cerebrospinal fluid (CSF) lymphocytosis (HaNDL syndrome) consists of recurrent headaches with focal neurological signs, which can include motor, sensory and aphasic symptoms. It is rare in the adult population but even more so in patients under the age of 18 years, with only 15 cases described in the paediatric population. Clinically, the focal neurological signs can be very alarming for the patient, the family as well as for the clinician, due to its recurring nature with the differential diagnosis of important and potential mortal causes. For this reason, other diagnoses must be ruled out before HaNDL syndrome can be reached. Once diagnosed, treatment is symptomatic with reassurance.

CASE PRESENTATION

A 14-year-old girl attended hospital after a week's history of recurrent, intense, occipital headaches lasting up to 12 h, with nausea and vomiting, accompanied by visual aura and photophobia. She had tried over-the-counter anti-inflammatory medication, to no avail. These headaches were shortly followed by episodes of expressive dysphasia lasting for 20 min, after which the symptoms resolved completely; the patient was symptom-free between episodes. She had no relevant medical history and was not on any medication. She had attended a clinic where basic blood tests and a MRI showed no significant abnormalities or signs of ischaemia, and was thus diagnosed with migraine. However, her symptoms worsened with the headaches

increasing in intensity and frequency (up to five a day), and waking the patient from sleep. Her neurological symptoms also persisted with new onset right-sided cheek and arm numbness of 2 h duration with complete recovery, which prompted her to present to hospital.

On physical examination, the patient was haemodynamically stable and afebrile, with a Glasgow Coma Score of 15 and no meningeal irritation. Expressive dysphasia was observed as well as agraphia without alexia, which resolved completely within a few hours. Cranial nerve examination was strictly normal as were upper and lower limbs, with intact reflexes. The patient was admitted to complete the aetiological study.

INVESTIGATIONS

Blood tests revealed no haematological abnormalities, and cerebral and supra-aortic angiographic MRIs were normal with no carotid dissection. During admission, the patient remained afebrile with recurrence and progression of her clinical symptoms of expressive dysphasia, right facial palsy, right sided hypoaesthesia and new onset right-sided weakness (4/5) with normal reflexes, every 2 days. Additionally, she experienced mild blurred vision. A moderate headache would follow, resolving completely within 6 h with no neurological sequelae. An EEG after sleep deprivation showed non-specific occasional slow multifocal discharges in the left hemisphere. Fundoscopic examination revealed bilateral papilloedema with the rest of the ophthalmological examination being normal. A lumbar puncture was performed with an opening pressure of 31 cm H₂O. The CSF was clear, transparent and non-traumatic. Laboratory analysis revealed pleocytosis of 490 cells (90% mononuclear), with normal glucose and proteins (40 mg/dL), and red blood cell count. Serology for neurotrophic viruses and bacteria was negative, as were oligoclonal bands and biopterin.

TREATMENT

Given the recurrent migraines with associated focal neurological signs with a pleocytosis in the CSF the diagnosis of syndrome of transient HaNDL syndrome was reached after excluding infective and other differential diagnoses. Treatment was started with acetazolamide with clinical improvement within a few days. The patient did not have any recurrent focal neurological symptoms and her headaches became mild and easily controlled with simple analgesia a few days after discharge, with complete cessation thereafter.

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OUTCOME AND FOLLOW-UP

A repeat funduscopy 1 month later showed no papilloedema. Acetazolamide treatment was continued for a further 2 weeks and stopped.

DISCUSSION

HaNDL syndrome was first described in 1980 by Swanson, Bartleson and Whisnant, who described seven patients with migrainous headache with pleocytosis in the CSF at the American Academy of Neurology. It has had numerous names in the past, such as migraine with pleocytosis and pseudomigraine with pleocytosis, but was coined HaNDL in 2004 by the International Classification of Headache Disorders.¹ Approximately 100 cases have been described in the literature,² and less than 15 in the paediatric population.³

The syndrome is characterised by (A) moderate to severe headaches with one or more transient neurological deficits lasting several hours, (B) the disappearance of attacks within 2 months, (C) a CSF lymphocytic pleocytosis (>15 white cells per μL), with negative reaction on bacteriological, viral and fungal test, (D) the absence of neuroradiological abnormalities other than transient decrease in cerebral blood flow and (E) the absence of epileptic waves on electroencephalographs.^{4 5} Focal neurological deficits are restricted to one hemisphere in most patients² and include hemiparaesthesia in three quarters of cases, dysphasia in half and hemiparesis in a little over half of patients, which usually last over 4 h (some up to 24 h) without leaving neurological sequelae and with symptom-free intervals.⁶ These episodes of headache and neurological deficits recur over fewer than 3 months.³ Over 90% of cases have increased protein in CSF (>250 mg/dL) and 60–70% have increased CSF pressure.^{2 7}

Migraine-aura-like visual symptoms are infrequent and are seen in less than 20% of cases,^{5 8} with most patients having no history of migraine.⁶ Papilloedema is occasionally present.^{7 9} Atypical presentations such as transient global amnesia,⁴ and confusion with decreased level of consciousness in paediatric cases^{8 10} and adult cases¹¹ have been reported, which may blur diagnostic clarity.

HaNDL syndrome is a benign and self-limiting disorder usually observed in young adults between 15–40 years of age,^{5 6} and has a higher incidence in men, contrary to the incidence of migraine, which is more common in women.^{4 6}

The differential diagnosis of a patient presenting with focal neurological deficits with headache include stroke; structural brain lesions; epileptic seizures; neuroinfectious diseases such as meningoencephalitis, Lyme borreliosis, neurosyphilis, mycoplasma and HIV meningitis; Mollaret's meningitis, encephalitis and neurolupus; familial hemiplegic migraine type 1 (FHM1); vasculitis of the central nervous system and Hashimoto's encephalopathy.^{12–14} Structural brain lesions, such as tumours, abscesses and white matter lesions were ruled out with the MRI scan that the patient had undergone before her admission. Neuroinfectious diseases were ruled out due to the history and clinical evolution as well as serological tests in serum and CSF. For example, during her admission, there was no nuchal rigidity, fever or reduced level of consciousness to suggest meningitis or encephalitis. Additionally, the patient was symptom-free with general well-being between attacks. Serological tests and CSF analysis for mycoplasma, syphilis and *Borrelia* were negative, as was HIV status. Herpes simplex virus and varicella virus were also negative, and FHM1 was not considered given the lack of family history and the lack of recurrence of symptoms once

discharged. Inflammatory markers as well as an autoimmune screen were negative. This with a normal cerebral MRI, the early and complete resolution of her symptoms with simple analgesia (without the use of steroids) and the lack of recurrence, would make the diagnosis of central nervous system vasculitis unlikely.

Owing to the variety of diseases it can mimic, HaNDL syndrome is a diagnosis of exclusion and can only be reached once these entities have been ruled out. Awareness of its existence can avoid unnecessary and potentially harmful investigations and therapies such as thrombolytic therapy.

The precise aetiology of HaNDL is still not fully understood, but theories have been proposed. An infectious hypothesis states that an infective process (probably viral) may trigger antibodies directed against neuronal or neurovascular entities such as the trigeminal terminal of the pachymeningeal blood vessels,³ or cause an aseptic leptomeningeal vasculitis,⁸ resulting in transient vascular headaches and neurological symptoms via mechanisms resembling cortical spread depression.^{4 6 11} Most patients report a prodrome of a viral-like illness, with 25% reporting this within 3 weeks prior to symptom onset.^{6 8} Isolated cases associated with an infectious trigger including human herpes virus six have been reported.¹⁵ While this theory may seem plausible due to the monophasic course and viral prodrome, none of the common viruses (herpes simplex virus 1–3, cytomegalovirus and varicella zoster virus, etc) and no other infectious diseases have been consistently found to trigger HaNDL syndrome. The autoimmune theory has also been proposed as a cause of the pathophysiology of HaNDL but this has been, up to the present day, inconsistent due to the lack of meningeal signs, the absence of long term chronicity and the absence of specific antibodies correlating with disease activity.

Neuroimaging is essential to rule out structural causes, and it is becoming increasingly apparent that there is evidence of cerebral hypoperfusion in HaNDL syndrome, using multimodal brain MRI showing delayed perfusion. MR-angiography has also shown discrepancies between cerebral vessel diameter, with the affected side having reduced diameter.¹⁶ Transcranial Doppler sonography during and after an attack has shown asymmetrical fluctuations in the middle cerebral artery blood flow velocity and pulsatility indicating that intracranial vasomotor changes similar to those found in migraine with aura may play a role in the pathogenesis of HaNDL.^{16 17}

On EEG, over 85% of patients have abnormal tracings on that side of the brain having the neurological deficit. The commonest findings are slow waves of δ or θ frequency, which can be focal or bilateral. On single-photon emission CT, the majority of reports have shown a decrease in cerebral blood flow on the side of origin of the neurological manifestations, which correspond to areas of focal slowing on EEG,^{3 11} although bilateral involvement may also occur.^{13 17} These alterations are usually detected in the acute phase but cases persisting up to several weeks after the event have been described too, relating to the cortical spread depression, which may explain the variability of clinical manifestations of the disease, even in the same person. In our patient, the EEG showed non-specific occasional slow multifocal discharges in the left hemisphere, which correspond to the right sided symptoms of dysphasia, right face paraesthesia and right arm weakness.

Treatment is symptomatic and supportive with all patients recovering within 1–84 days with only a few patients experiencing recovery.^{2 18} Because the disease is self-limiting, education and reassurance of the patient and family are very important. Lumbar puncture opening pressure and papilloedema have been

described to improve with acetazolamide treatment.² Our patient improved with acetazolamide, but one could speculate whether this was directly due to treatment or due to the natural course of the disease.

In conclusion, HaNDL is a benign self-limiting, underdiagnosed entity that may mimic a variety of diseases including those with poor prognosis. Awareness of its existence can avoid unnecessary and potentially harmful investigations and therapies.

Learning points

- ▶ Headache and neurological deficits with cerebrospinal fluid lymphocytosis syndrome is a rare, benign and underdiagnosed disorder that is becoming increasingly recognised.
- ▶ It is described as a moderate to severe headache with focal neurological signs, accompanied by pleocytosis in the cerebrospinal fluid.
- ▶ It can mimic a variety of diseases including stroke, structural brain lesions, infections of the central nervous system and vasculitis, making it a diagnosis of exclusion.
- ▶ The exact pathophysiology is still not fully understood, although it is similar to migraine.
- ▶ Treatment is symptomatic with an excellent prognosis.

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Competing interests None declared.

Patient consent Obtained.

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