Headache, confusion, and behavioral changes - a HaNDL case report

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ABSTRACT

Background: The clinical syndrome of headache and neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) is recognized as a self-limiting condition consisting of discrete episodes of neurological deficit associated with moderate to severe headache. The spectrum of neurological features most commonly include aphasia, sensory, and motor disturbances. However, confusion and agitation has also been described.

Case Presentation: We present an unusual case of a 28-year-old male with recurrent hospital presentations for headache, confusion, and other neurological stigmata over a period of 15 days, culminating in a diagnosis of HaNDL following extensive investigations. He was treated empirically for viral encephalitis initially; however, there were no positive results on virology screening. In addition, autoimmune screens were also negative. He was then managed symptomatically and discharged from hospital with resolution of symptoms thereafter.

Conclusion: The differential diagnoses for transient acute confusional disorders remain expansive, with HaNDL being one of the many rare causes. Rigorous testing is required to exclude infective, inflammatory, ischemic, structural, or iatrogenic pathology, whil HaNDL primarily remains a diagnosis of exclusion.

Keywords: HaNDL, confusion, headache, behavioral changes, CSF lymphocytosis, neurological deficits.

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Background

We describe a case of an otherwise well 28-year-old male with recurrent presentations to a metropolitan Queensland hospital for headache, confusion, reduced Glasgow Coma Scale (GCS), and a constellation of other neurological signs subsequently diagnosed as the syndrome of headache and neurologic deficits associated with cerebrospinal fluid (CSF) lymphocytosis (HaNDL).

The syndrome was first described in 1981 by Bartleson et al. [1] It has also been known as pseudomigraine with transient neurological symptoms and lymphocytic pleocytosis (PMP) before the acronym of HaNDL was attributed to the syndrome in 1995 by Berg and Williams [2].

The International Classification of Headache Disorders [3] lists HaNDL as a rare disorder within the non-infectious inflammatory diseases' category. It has been described in both sexes, ranging in age from 7 to 53 years, with a male predominance [4]. The clinical presentation consists of several discrete episodes of neurological deficit accompanied or followed by moderate to severe headache [5]. Aphasia, sensory, and motor deficits are most common, although changes in behavior have also been described [5,6]. The condition is self-limiting, lasting from 1 to 12 weeks [5,6]. Some case series have reported associated fevers and viral prodrome [7]. CSF pleocytosis (10-700 cells/mm^3) with a lymphocytic predominance and a raised protein level are seen in most cases. Also, CSF pressure (up to 400 mm CSF) is elevated in 50% of the cases and transient non-epileptiform electroencephalogram (EEG) changes have also been described [8]. Bacterial, viral, fungal, and autoimmune screens must return negative to allow for diagnosis of exclusion [2-8].

Neuroimaging is essential to rule out structural causes. Routine computer tomography (CT), magnetic resonance imaging (MRI), and angiography are invariably normal when performed between episodes. However, studies have increasingly shown cerebral hypoperfusion if performed within a discrete event [9]. Magnetic resonance angiography (MRA) has also shown discrepancies in cerebral vessel diameter, with a smaller caliber in the affected side [9]. Transcranial doppler sonography (TDS) performed during and after an attack has shown asymmetrical fluctuations in the middle cerebral artery blood flow velocity and pulsatility. These fluctuations indicate intracranial vasomotor changes, which may play a role in the

pathogenesis of HaNDL [9,10]. On single-photon emission CT, the majority of reports have shown a decrease in cerebral blood flow on the side corresponding to the neurological stigmata, which correlates to the areas of slowing on EEG [3,10]. More than 85% of the patients have abnormal tracings on the side of the brain corresponding to the neurological deficits. The commonest finding is slow wave frequency, either focal or diffuse [4].

The etiology and pathophysiology remain poorly understood. However, there have been several hypotheses. The first of which was proposed to be a migraine-like illness secondary to central nervous system inflammation [8]. Later, some postulated that immunological dysfunction induces pro-inflammatory markers, thereby generating anti-neuronal/neurovascular antibodies, causing a vasculitis-related cortical spreading depression [8]. Another theory is that there are changes in neuronal metabolism, with cerebral hypoperfusion being an epiphenomenon of the syndrome [9]. Cruz et al. [12] suggested an association between vasomotor alterations and the pathophysiology of HaNDL, following findings of diffuse slow activity on EEG and increased blood flow velocity in TDS.

Due to the rarity and transient nature of HaNDL, treatment is largely supportive care, with no current recommended therapeutic strategies. Short-term use of steroids has been suggested, particularly if the patient has persistently raised intracranial pressures [13].

Case Presentation

A 28-year-old male presented to a metropolitan hospital via ambulance for the fourth time in 9 days. On this occasion, he had a reduced GCS of 10 and confusion. His wife found him lying on the floor unresponsive, pale, diaphoretic with a blank stare, rhythmic tongue movements and dilated pupils. This episode lasted for 15 minutes. She also reported that he was unable to recognize family members earlier in the day. While in the emergency department (ED), he had another similar episode lasting for 10 minutes. The provisional diagnosis was absence seizures; therefore, he was loaded with levetiracetam. Despite this, the patient became increasingly agitated and combative in ED, resulting in the decision for rapid sequence induction and intubation to facilitate further investigation and management. With subsequent care provided in the intensive care unit (ICU), he came to the attention of the authors of this report.

Collateral history was obtained from the patient's partner. She reported no known past medical history, specifically no history of migraine, no regular medications, and no known allergies. The patient was described as a fit, healthy, independent male who was employed as an electrical engineer. There was no history of recreational drug use or sexually transmitted diseases. He lives with his wife and newborn son. There was no history of antecedent respiratory symptoms, fever, or sick contacts. There was no history of recent international travel. The last domestic travel was to the Pilbara region in Western Australia and Weipa in North Queensland in the month prior to onset of symptoms.

The patient had presented to the hospital on three other occasions within a 9 days time span, prior to his presentation described above. His first presentation was for a 6-day history of intermittent, severe, retro-orbital headache associated with nausea, vomiting, and dizziness. This was thought to be the results of a viral illness and he was discharged with simple analgesia.

He presented for a second time the following day with an overall worsening of his symptoms, in addition to occasional blurred vision, unspecific paraesthesia, and intermittent confusion. He also complained of intermittent slurred speech and expressive dysphasia, unable to complete a sentence or write appropriate text messages. He was admitted to the short stay unit in the ED for further investigation with a CT head and lumbar puncture (LP). The CT head was unremarkable. LP showed a white cell count of 250 × 10^6/l (99% monocytes); protein of 1,600 mg/l and glucose of 4.0 mmol/l. Opening pressure was not obtained (Table 1). The patient was subsequently admitted to a medical ward with the provisional diagnosis of viral meningitis/encephalitis. The patient was managed with a 3-day course of acyclovir (10 mg/kg 8 hourly), while the full panel of LP results were pending. These returned showing negative virology. He was discharged 4 days later with advice for regular simple analgesia, despite complaints of occasional headache on mobilization.

He re-presented for a third time later the day of discharge with a worsening headache, blurred vision, and subjective photophobia. His wife found him acutely confused, rolling around the lounge with slurred speech. He was readmitted under a general medical physician for further investigation and management. MRI of the head was completed and reported as a normal study. He had intermittent headache over the 4-day observation period with no further behavioral changes or neurological deficits. The patient was subsequently discharged with an outpatient referral to a psychiatrist for consideration of differential diagnoses, including psychosomatic disorder.

One day after discharge, he presented the fourth time. The patient was acutely confused in ED when reviewed prior to intubation, with a GCS of 10 (E4V2M4). He was curled up in bed, laughing inappropriately, making incomprehensible sounds, and could not recognize his wife. Later he became increasingly agitated and combative, requiring physical restraints following failed verbal de-escalation. His hemodynamics remained robust and limited neurological examination showed no evidence of meningism or focal neurological deficit. The remainder of his physical examination showed no positive cardiovascular, respiratory, gastrointestinal, genito-urinary, or dermatological findings.

Table 1. *CSF results of the patient. The first LP was performed during his second admission, and the second LP was performed during his fourth admission. There is an increase in both the number of WBC and total protein between the first and second result.*

IN	1st LP (Medical Admission)	2nd LP (ICU admission)
Appearance	Clear and colorless	Clear and colorless
WBC (× 10^6/l)	250 (99% mononuclears)	279 (99% mononuclears)
RBC (× 10^6/l)	0	0
Protein (mg/l)	1,600	2500
Glucose (mmol/l)	4.0	4.2
Opening pressure (cm H_20)	-	17
Gram stain	No organism seen	No organism seen
Indian Ink	Negative	Negative
Cryptococcal Ag (titer)	Non-reactive	Non-reactive
Culture	No growth	No growth

While in the ICU, the patient remained intubated and sedated with a combination of propofol and fentanyl to allow for ongoing investigation. A second MRI and LP (Table 1) were performed. The MRI was unremarkable, while the LP showed marked lymphocytosis (279 × 10^6/l) and elevated protein (2500 mg/l). The patient was commenced on 2 g ceftriaxone 12 hourly, 900 mg acyclovir 8 hourly, and 10 mg dexamethasone 6 hourly. Additional investigations performed included Herpes Simplex Virus polymerase chain reaction (PCR), Lyme disease serology, varicella zoster, adenovirus, enterovirus, thyroid function, autoimmune, multiple myeloma, hepatitis, human immunodeficiency virus, tuberculosis, measles/mumps/rubella, encephalitis antibody, anti-neutrophil, anti-neuronal antibody screen, N-Methyl-D-aspartic acid receptor antibodies, anti-Voltage Gated Potassium Channel antibodies, and urine toxicology screen. CT head, neck, chest, abdomen, and pelvis were performed, in addition to an ultrasound of the testes to exclude primary malignancy and potential paraneoplastic syndrome. These investigations were all normal. Following discussion with a neurologist at our tertiary referral center, the patient was commenced on immunoglobulin therapy [Immunoglobulin therapy (IVIG)] - normal human immunoglobulin 10%, 40 g daily, 5 days] and methylprednisolone (1 g, once daily, 5 days), in addition to regular levetiracetam (1,000 mg, twice daily). The patient was also reviewed by an infectious disease consultant, who had considered Epstein-Barr Virus, Murray Valley, Flavivirus, Rickettsia, and Kunjin virus encephalitis as differential diagnoses, but the test results of these were also unremarkable. All antimicrobials and antivirals were ceased on day 3 of admission when the CSF screen returned as normal.

The patient was subsequently transferred to the ICU of our tertiary referral center on day 4 of this admission to allow for EEG, which is not available at our institution. The EEG showed mild to moderate diffuse cerebral dysfunction of non-specific etiology. However, no epileptiform discharges or electrographic seizures were seen.

He was extubated on day 4 of admission and transferred to the care of a neurology team. Fluorodeoxyglucose positron emission tomography scan was performed and reported as normal. A follow-up EEG performed 2 days post-extubation showed diffuse slowing with some preserved reactivity consistent with mild to moderate cerebral dysfunction. The slowing was more prominent on the left, therefore raising the possibility of an element of focal dysfunction. No epileptiform activity was seen. In summary, the patient completed a 3-day course of methylprednisolone and 5 days of IVIG. He was discharged on day 10 of his fourth presentation with 1,000 mg levetiracetam twice daily. A multidisciplinary team review concluded that he should have a repeat EEG in 4 weeks, followed by a neurology outpatient appointment in 2 months. It was recommended for him to continue levetiracetam for at least 6 months. The patient had no further hospital presentations following discharge. On follow-up phone call, he had experienced no further episodes at the time this report was completed.

Discussion

Berg and Williams [2] first proposed a diagnostic criterion for HaNDL of severe headache, temporary neurologic deficits, CSF lymphocytosis, and a self-limiting clinical course. Associated features included increased CSF proteins, increased intracranial pressure, and transient focal non-epileptiform EEG changes with occasional viral prodrome or fever. Currently, the 3rd edition of the International Classification of Headache Disorders, describes the diagnostic criteria (Figure 1):

Adapted from The International Classification of Headache Disorders [3].

This case highlights the difficulty in recognizing HaNDL, given that it was only identified on his fourth presentation. Although confusion [5-8,14-16] has been commonly reported within HaNDL literature, there are few described cases of behavioral changes. The patient had episodes of agitation, aggression, and erratic behavior over the course

A.	Both of the following:
	1. Accompanied or shortly preceded by onset of at least one of the following transient neurological deficits lasting >4 hours
	(a) Hemiparesthesia
	(b) Dysphasia
	(c) Hemiparesis
	2. Associated with CSF PMP (>15 white cells per µl), with negative etiological studies
B.	Evidence of causation demonstrated by either or both of the following:
	1. Headache and transient neurological deficits have developed or significantly
	2. worsened in temporal relation to onset or worsening of the CSF PMP, or led to its discovery
	3. Headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF PMP
C.	Not better accounted for by another ICHD-3 diagnosis

Figure 1. *Episodes of migraine-like headache fulfilling criteria B and C.*

of his illness, thereby making his presentation uncommon even within the small sample of reported HaNDL cases. Additionally, while confusion is often reported, it is not included in the current diagnostic criteria for HaNDL. If corroborated by further case reports, confusion and behavioral changes may be considered for inclusion as the diagnostic criteria. Additionally, the sensitivity and specificity of these symptomology may be investigated further.

Conclusion

In conclusion, the differential diagnoses for transient acute confusional disorders remain vast, with HaNDL being one of many rare causes. Rigorous testing is required to exclude infective, inflammatory, ischemic, structural, or iatrogenic pathology and HaNDL remains primarily a diagnosis of exclusion.

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What is new?

HaNDL is recognized as a self-limiting condition consisting of discrete episodes of neurological deficit associated with moderate to severe headache. Although confusion has been commonly reported within HaNDL literature, there are few described cases of behavioral changes, as seen in our patient.

List of Abbreviations

CSF	Cerebrospinal fluid
CT	Computer tomography
ED	Emergency department
EEG	Electroencephalogram
GCS	Glasgow Coma Scale
HaNDL	Headache and neurological deficits and cerebrospinal fluid lymphocytosis
ICU	Intensive care unit
IVIG	Immunoglobulin therapy
LP	Lumbar puncture
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PMP	Lymphocytic pleocytosis
TDS	Transcranial Doppler sonography

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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Summary of the case

1	**Patient (gender, age)**	28-year-old male
2	**Final diagnosis**	Headache and neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL)
3	**Symptoms**	Headache, confusion, and other neurological stigmata over a period of 15 days
4	**Medications**	Patient completed a 3-day course of methylprednisolone and 5 days of IVIG as well as discharged with anti-epileptics for a period of 6 months
5	**Clinical procedure**	Lumbar Puncture
6	**Specialty**	Intensive Care Medicine