Case Report

Headache associated with neurological deficits and cerebrospinal fluid lymphocytosis syndrome with delayed neurological deficits mimicking chronic lymphocytic meningitis: A diagnostic challenge from a tuberculosis-endemic region

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ABSTRACT

Headache associated with Neurological Deficits and Cerebrospinal Fluid Lymphocytosis (HaNDL) syndrome is a rare, self-limiting disorder that often mimics infectious, inflammatory, and vascular diseases. We report a 42-year-old man with recurrent severe unilateral headaches accompanied by nausea, photophobia, and phonophobia. Initial investigations were unremarkable, and he was treated as status migrainosus with only transient benefit from corticosteroids. Cerebrospinal fluid (CSF) analysis later showed lymphocytic pleocytosis and elevated protein, raising suspicion for tuberculous meningitis despite negative microbiological studies. Antitubercular therapy was initiated elsewhere without clinical improvement. Repeat neuroimaging and autoimmune evaluation were normal. During hospitalization, he developed transient episodes of confusion, dysphasia, and left-sided sensory symptoms without radiological abnormalities. A diagnosis of HaNDL syndrome was established based on recurrent migraine-like headaches, transient neurological deficits, CSF lymphocytic pleocytosis, and exclusion of alternative causes. The patient improved with corticosteroid therapy and remained symptom-free at 1-year follow-up.

Key words: Aseptic meningitis, Cerebrospinal fluid lymphocytosis, Headache associated with neurological deficits and cerebrospinal fluid lymphocytosis syndrome, Migraine, Transient neurological deficits, Tuberculous meningitis mimic

Headache associated with Neurological Deficits and Cerebrospinal Fluid Lymphocytosis (HaNDL) syndrome is characterized by recurrent migraine-like headaches associated with transient neurological deficits and cerebrospinal fluid (CSF) lymphocytic pleocytosis. The syndrome was first described by Bartleson *et al*. in 1981 and was later termed HaNDL syndrome by Berg and Williams [1,2]. According to the International Classification of Headache Disorders, 3rd edition, the diagnosis is based on episodes of moderate-to-severe migraine-like headache associated with transient neurological deficits lasting more than 4 h, CSF lymphocytic pleocytosis (>15 cells/μL), and exclusion of infectious, vascular, neoplastic, and autoimmune etiologies (Table 1) [3]. HaNDL syndrome remains exceedingly uncommon. A 2023 systematic review identified only 93 patients reported across 57 studies [4].

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Because of its rarity and overlap with numerous neurological conditions, including acute stroke, viral meningitis, tuberculous meningitis, autoimmune encephalitis, and complicated migraine, the syndrome is frequently underrecognized and misdiagnosed [5,6]. Neuroimaging is usually normal, although transient perfusion abnormalities have occasionally been reported during symptomatic episodes [7].

CASE REPORT

A 42-year-old man presented with persistent daily severe headaches beginning around 15 June 2025. The headaches were unilateral, involving either side of the head, predominantly affecting the occipital, parietal, and temporal regions, and associated with nausea, irritability, photophobia, phonophobia, and occasional ipsilateral peri-orbital pain. There was a partial relief with non-steroidal anti-inflammatory drugs. There was no history of fever, cough, constitutional symptoms,

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Table 1: Fulfillment of ICHD-3 diagnostic criteria for HaNDL syndrome

ICHD-3 criterion	Findings in the present case
Episodes of moderate-to-severe migraine-like headache	Recurrent severe unilateral occipito-parieto-temporal headaches associated with nausea, photophobia, and phonophobia
Transient neurological deficits temporally related to headache episodes	Episodes of confusion, dysphasia, transient word-finding difficulty, and left-sided numbness involving upper and lower limbs
CSF lymphocytic pleocytosis (>15 cells/μL)	Initial CSF: 200 cells/mm^3 with 90% lymphocytes
No alternative explanation after appropriate investigations	Extensive infectious, autoimmune, vascular, and structural evaluation negative
Self-limiting clinical course	Complete clinical recovery with no recurrence during 1-year follow-up

CSF: Cerebrospinal fluid, HaNDL: Headache associated with neurological deficits and cerebrospinal fluid lymphocytosis, ICHD-3: International classification of headache disorders, 3rd edition

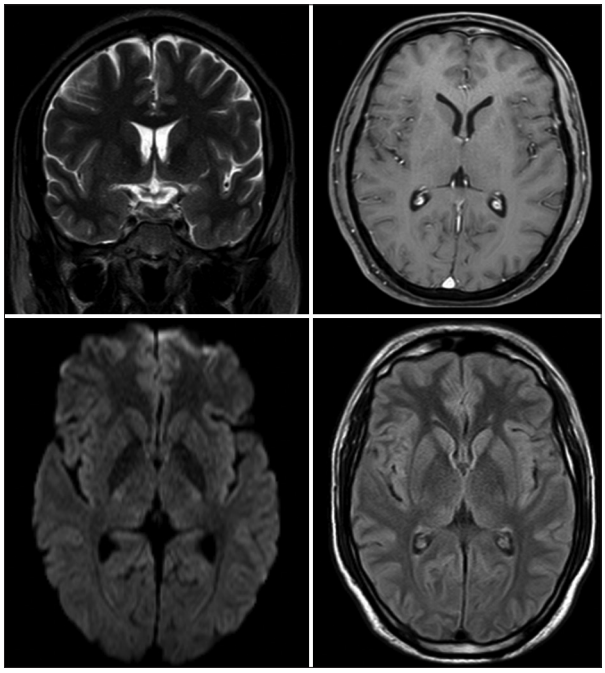


Figure 1: Magnetic resonance imaging brain with contrast performed during initial evaluation demonstrating no structural abnormality

seizures, visual disturbances, diplopia, limb weakness, altered sensorium, redness of eyes, lacrimation, or nasal congestion. No history of travel to Lyme endemic areas and bull's-eye skin rash. No history of close contact with animals.

Initial evaluation on 24 June 2025 revealed no focal neurological deficits. Magnetic resonance imaging (MRI) brain with contrast was normal (Fig. 1). Routine blood investigations, including complete blood picture, metabolic profile, erythrocyte sedimentation rate, and C-reactive protein, were within normal limits.

Because of a persistent severe headache, the patient was admitted between 26 June and 29 June 2025 and was diagnosed with status migrainosus. Intravenous dexamethasone produced substantial improvement. However, severe headaches recurred after discharge, necessitating admission to another hospital, where he again improved transiently with corticosteroid therapy. Due to persistent symptoms, further investigations were undertaken. Computed tomography (CT) brain and cerebral angiography (Fig. 2) were normal. CSF demonstrated 200 cells/mm^3 with 90% lymphocytes and an elevated protein concentration (55 mg/dL). CSF glucose was normal (50 mg/dL). CSF Gram stain, bacterial culture, India ink preparation, and tuberculosis (TB) GeneXpert testing were negative. Despite the absence of clinical features strongly suggestive of tuberculous meningitis, the combination of CSF lymphocytic pleocytosis and elevated protein resulted in empirical initiation of antitubercular therapy (ATT) at an outside institution. The patient failed to improve clinically despite ATT and was subsequently evaluated by the Neurology Board at KIMS Seethammadhara. Considering the atypical clinical presentation for tuberculous meningitis, ATT was discontinued. Further investigations, including antinuclear antibody profile, aquaporin-4 antibody, and myelin oligodendrocyte glycoprotein antibody testing, were negative (Table 2).

The patient was admitted again on July 28th, 2025, for further evaluation. On examination, blood pressure was 122/80 mmHg. He was conscious, alert, and oriented. There was no dysarthria, cranial nerve involvement, neck stiffness, papilledema, cerebellar signs, or focal motor deficits. Repeat MRI brain with contrast (Fig. 3) and MRI cervical spine (Fig. 4) did not reveal any abnormality. Repeat CSF analysis demonstrated 8 lymphocytic cells/mm^3 with persistently elevated protein (56 mg/dL) and normal glucose concentration (51 mg/dL). CSF BioFire meningitis panel and TB polymerase chain reaction (PCR) were negative. CSF opening pressure was 60 mm H_2O.

At this stage, the presence of persistent headache, sterile lymphocytic CSF pleocytosis, and repeatedly normal neuroimaging raised the possibility of an aseptic inflammatory process. HaNDL syndrome was considered among the differential diagnoses; however, the absence of neurological deficits precluded a definitive diagnosis.

During hospitalization, the clinical picture evolved. The patient began experiencing intermittent episodes of confusion, transient word-finding difficulty, dysphasia, and numbness involving the left upper and lower limbs. Individual episodes lasted several hours and resolved spontaneously without residual neurological deficit. Repeat MRI brain performed during symptomatic periods (Fig. 5) remained normal and did not demonstrate evidence of ischemia, demyelination, encephalitis, or vasculitis. Other differential diagnosis considered and excluded were migraine/hemiplegic migraine (in view of CSF pleocytosis), acute stroke, subarachnoid hemorrhage, and reversible cerebral vasoconstriction syndrome (normal neuroimaging on multiple times,

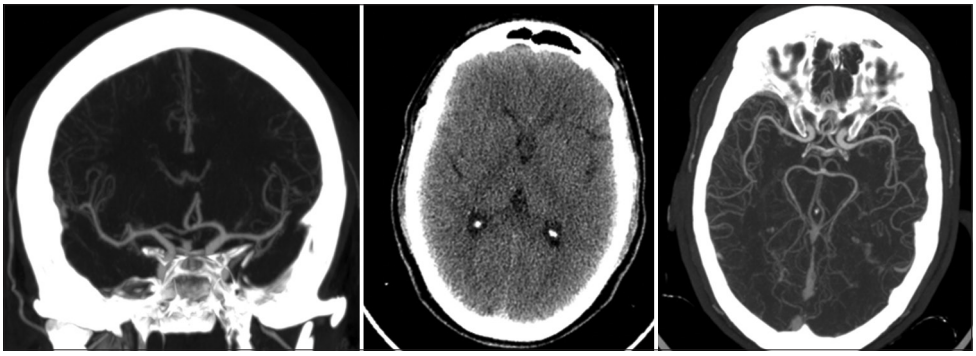


Figure 2: Computed tomography cerebral angiography demonstrating normal intracranial arterial circulation without evidence of vasculitis, aneurysm, or vascular malformation

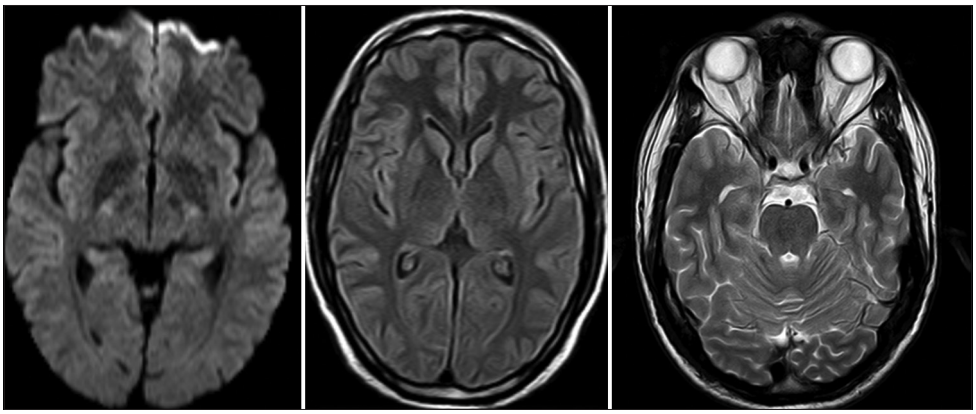


Figure 3: Repeat magnetic resonance imaging brain with contrast showing no parenchymal, meningeal, or vascular abnormalities

Table 2: Summary of diagnostic investigations

Investigation	Findings
Complete blood count	Normal
Metabolic profile	Normal
ESR and CRP	Normal
MRI brain with contrast (Initial)	Normal
CT Brain	Normal
CT cerebral angiography	Normal
Cerebral angiography	Normal
CSF analysis 1	200 cells/mm^3 (90% lymphocytes), protein 55 mg/dL, glucose 50 mg/dL
CSF gram stain	Negative
CSF culture	Negative
India ink preparation	Negative
TB GeneXpert	Negative
ANA profile	Negative
Aquaporin-4 Antibody	Negative
MOG antibody	Negative
MRI brain with contrast (Repeat)	Normal
MRI cervical spine	Normal
CSF analysis 2	8 lymphocytes/mm^3, protein 56 mg/dL, glucose 51 mg/dL
CSF BioFire meningitis panel	Negative
CSF TB PCR	Negative
Repeat MRI during neurological symptoms	Normal

CSF: Cerebrospinal fluid, TB: Tuberculosis, PCR: Polymerase chain reaction, MOG: Myelin oligodendrocyte glycoprotein, MRI: Magnetic resonance imaging, ANA: Antinuclear antibody, CT: Computed tomography, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein

normal CT angio), central nervous system (CNS) vasculitis, granulomatosis, and neoplastic arachnoiditis (normal contrast MRI brain).

The delayed onset of transient neurological deficits alongside recurrent migraine-like headaches, CSF lymphocytic pleocytosis, normal neuroimaging, and exclusion of alternative diagnoses completed the classical clinical picture of HaNDL syndrome, establishing the diagnosis. The patient received corticosteroids for 1 week with marked clinical improvement. Headaches resolved, neurological deficits disappeared completely, and no further episodes occurred. He remained asymptomatic during 1 year of follow-up, with no recurrence or new neurological manifestations.

DISCUSSION

HaNDL syndrome is characterized by the triad of migraine-like headaches, transient neurological deficits, and CSF lymphocytic pleocytosis [1-3]. The syndrome remains underdiagnosed because of its rarity and its close resemblance to infectious, vascular, inflammatory, and autoimmune disorders of the CNS [3]. The present case illustrates several important diagnostic challenges associated with this uncommon disorder.

The diagnosis of HaNDL syndrome is based upon the presence of migraine-like headaches, transient neurological deficits, CSF lymphocytic pleocytosis, and exclusion of alternative etiologies [3]. Our patient fulfilled all established diagnostic criteria. He developed severe migraine-like headaches associated with nausea, photophobia, and

phonophobia, demonstrated CSF lymphocytic pleocytosis with elevated protein concentration, and subsequently developed transient neurological deficits consisting of confusion, dysphasia, and unilateral sensory symptoms. Extensive infectious, autoimmune, vascular, and structural evaluations were negative.

The most important and unusual feature of this case was the delayed appearance of neurological deficits. In many reported cases, headache and focal neurological symptoms occur concurrently or within a short interval of each other [5]. In contrast, our patient initially presented only with persistent migraine-like headache and CSF lymphocytic pleocytosis. Although HaNDL syndrome was considered among the differential diagnoses after exclusion of common causes, the absence of transient neurological deficits prevented diagnostic confirmation. Several weeks later, the patient developed episodes of confusion, dysphasia, and hemisensory symptoms, thereby completing the characteristic clinical triad.

This delayed evolution of symptoms represents a significant diagnostic pitfall. Clinicians may prematurely exclude HaNDL syndrome when neurological deficits are absent during the early phase of disease. Our case demonstrates that the syndrome may evolve sequentially rather than presenting with the complete triad at onset. Recognition of this possibility is important because delayed neurological manifestations can lead to repeated hospital admissions, diagnostic uncertainty, and unnecessary investigations.

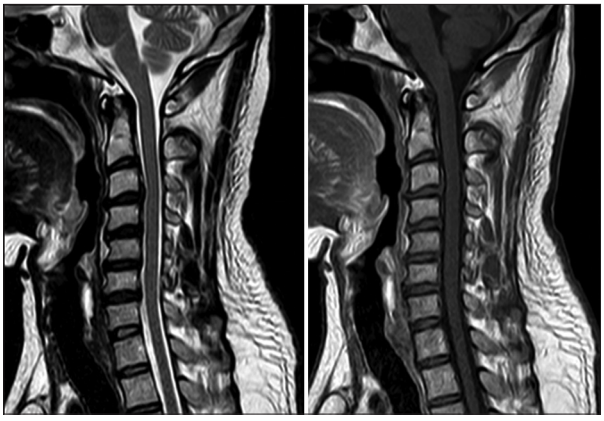


Figure 4: Magnetic resonance imaging cervical spine demonstrating no demyelinating, inflammatory, or compressive lesion

Another notable feature of this case was the extensive diagnostic workup performed before the diagnosis became evident. Despite extensive investigation, no alternative explanation for the patient's symptoms was identified. Such diagnostic evaluations are common because HaNDL frequently mimics serious neurological disorders [6]. The differential diagnosis in this patient was particularly challenging because the CSF findings demonstrated marked lymphocytic pleocytosis with elevated protein concentration. In countries such as India, where TB remains endemic, these findings frequently raise a strong suspicion of tuberculous meningitis. Consequently, empirical ATT was initiated. However, several features argued strongly against tuberculous meningitis. Furthermore, repeated microbiological investigations, including TB GeneXpert and TB PCR, remained negative. These atypical features prompted reconsideration of the diagnosis and discontinuation of treatment.

This aspect of the case is particularly relevant for clinicians practicing in TB-endemic regions. HaNDL syndrome should be considered in patients with sterile lymphocytic pleocytosis and migraine-like headaches when the clinical picture is inconsistent with chronic infectious meningitis. Failure to recognize the syndrome may expose patients to unnecessary antimicrobial therapy, adverse effects, and healthcare costs.

Treatment of HaNDL syndrome remains largely supportive because the disorder is generally self-limiting [6]. Analgesics, antiemetics, and migraine-directed therapies are commonly used. Corticosteroids have been reported to provide symptomatic benefit, although evidence remains limited to case reports and small series [8]. Our patient demonstrated marked clinical improvement following a short course of corticosteroids. Although spontaneous resolution cannot be excluded, rapid improvement after corticosteroids may support an inflammatory component.

To the best of our knowledge, reports of HaNDL syndrome from India remain uncommon. The combination of delayed neurological deficits, repeated

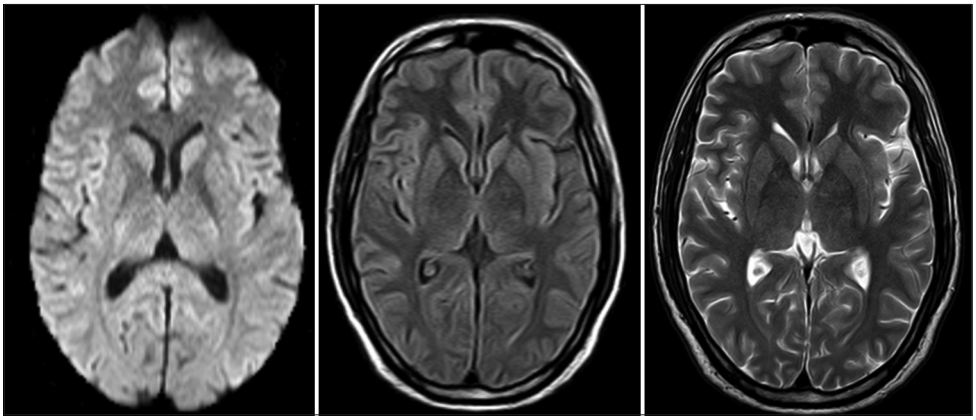


Figure 5: Magnetic resonance imaging brain obtained during an episode of transient neurological deficit showing no acute ischemic, inflammatory, or structural abnormality

normal neuroimaging, chronic meningitis mimicry, unnecessary ATT, and complete recovery makes this case particularly educational.

CONCLUSION

HaNDL syndrome is a rare but important differential diagnosis in patients presenting with recurrent migraine-like headaches and CSF lymphocytic pleocytosis. The present case demonstrates that neurological deficits may appear late in the disease course, delaying diagnostic confirmation and resulting in repeated investigations and unnecessary treatment. Awareness of this uncommon disorder is particularly important in TB -endemic regions. Early recognition can prevent unnecessary therapy, repeated investigations, and diagnostic uncertainty.

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