HaNDL with care

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Abstract

Headache with neurological deficit and cerebrospinal fluid (CSF) lymphocytosis (HaNDL) syndrome is an important diagnosis to consider in patients presenting with the relevant features to acute medicine. Investigations should aim to exclude more serious differential diagnoses such as infectious, inflammatory and neoplastic causes prior to making a formal diagnosis of HaNDL. Increased awareness and early consideration of HaNDL would help to avoid unnecessary prolonged courses of antimicrobial therapy and invasive investigations such as cerebral angiography.

Keywords:

HaNDL, Headache, Migraine, CSF lymphocytosis

Key points

1. HaNDL syndrome is important to consider in patients presenting to acute medicine with headache and neurological deficits, who are found to have a lymphocytosis in the CSF.
2. Careful history, examination and investigation should be performed to exclude infections, inflammatory disorders and neoplasms that can also cause headache, focal neurological signs and CSF lymphocytosis
3. Increased awareness and early consideration of the diagnosis would help to avoid prolonged use of inappropriate antimicrobials and unnecessary invasive investigations.

Introduction

Headache with neurological deficit and cerebrospinal fluid lymphocytosis (HaNDL) syndrome is a benign condition which has three major features, as described by the acronym. HaNDL syndrome has been recognised since the 1980s and has been previously known as pseudomigraine with lymphocytic pleocytosis (PMP). Patients usually present in the third or fourth decade of life and there is a male preponderance (male : female ratio 3:1).[1,2] The majority of cases may have no past medical history of migraine.[1]

The aetiology of this condition is still unknown. Twenty-five percent of patients have been found to suffer a prodromal flu-like illness 3 weeks prior to the event. During the event patients may suffer nausea, vomiting, photophobia, phonophobia and fever, but notably there is an absence of meningism. HaNDL syndrome is typically a monophasic illness and the episode can last from hours to weeks but an average of fourteen days has been reported.[1] We report a case of HaNDL syndrome.

Case report

A 28 year old healthy man reported to our emergency department with a two-week history of headaches that were left sided, retro-orbital and throbbing in nature. He had associated photophobia and nausea. He presented because of a much more severe bilateral frontal headache which had developed suddenly that day. On questioning, he had been aware of numbness and paraesthesia in his right hand lasting several hours. A past medical history of migraine was noted. He was on no regular medication, was a non-smoker and denied excess alcohol or illicit substance use. He was apyrexial, with no neck stiffness. He was alert and orientated. Neurological examination was normal.

He initially had a CT head to exclude a subarachnoid haemorrhage, given the sudden headache. This was normal. Laboratory blood tests showed a raised white blood cell count of 14.0 x 10^9/L (neutrophils 10.8 x 10^9/L), with a normal CRP and ESR. He then went on to have a lumbar puncture, which showed a white cell count (WCC) of 69 /mm^3, (no differential was available) a red blood cell count (RBC) of 11/mm^3, cerebrospinal fluid (CSF) protein of 1.08g/L (normal 0.10 – 0.40 g/L) and CSF glucose of 3.0 mmol/L with no bacterial growth. By day 8 since presentation the CSF WCC had increased to 436/mm^3 (95% lymphocytes) and the CSF protein to 1.68g/L. Following the lumbar puncture results, he was initially treated with IV acyclovir for viral meningitis.

Further investigations including autoimmune screen, HIV, treponema, leptospirosis and borrelia serology and CSF and viral (HSV, VZV, EBV, CMV, enterovirus, parechovirus) PCR were negative.

Magnetic resonance imaging (MRI) of the brain and MRI brain angiography were performed

Biography

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Table 1. Summary of CSF results

Day	CSF protein (g/L)	CSF glucose (mmol/L)	Plasma glucose (mmol/L)	CSF WCC (/mm^3)	CSF RBC (/mm^3)	Opening pressure (cm H_2O)
1	1.08	3.0	n/a	69	11	33
8	1.68	2.5	n/a	436 (95% lymphocytes)	12	n/a
13	0.75	3.1	4.7	189 (100% lymphocytes)	15	39
33	0.54	2.9	4.4	4	<1	n/a

to exclude cerebral vasculitis or other intracranial inflammatory pathology and were also normal.

He continued to have an ongoing, severe left sided throbbing headache with intermittent exacerbations associated with nausea and photophobia, but remained well with no fever or other systemic symptoms. Based on the clinical picture above and the negative investigation results, he was diagnosed with HaNDL and the antimicrobials were stopped. He was treated with propranolol. The headaches subsided and he was discharged home. He remained clinically well and a repeat lumbar puncture on day 33 revealed resolution of the CSF abnormalities, with a CSF WCC of 4/mm^3, RBC of <1/mm^3, protein of 0.54g/L and glucose of 2.9 mmol/L (plasma glucose 4.4 mmol/L) (Table 1).

Discussion

HaNDL syndrome is a relatively rarely recognised self-limiting condition that presents with headache, neurological deficit and cerebrospinal fluid lymphocytosis. Although the aetiology and pathogenic mechanisms that take place are still unknown, several theories exist. These include atypical migraine,[3] a calcium channelopathy[4] and a viral trigger leading to cortical spreading depression with subsequent trigeminovascular activation and a sterile leptomeningeal inflammatory process.[1,3] A recent study has implicated antibodies to a subunit of the T-type voltage-gated calcium channel, CACNA1H, suggesting an immune mediated cause in some cases.[5]

A set of diagnostic criteria have been delineated by The International Classification of Headache Disorders: 2nd Edition. (Box 1).[6]

The headache described is often a moderate to severe throbbing headache, with migrainous features and may be bilateral or hemicranial.[1] Although the majority have no past history of headache 24% of males and 31% females have suffered from headaches previously.[1] The headache has been reported to last from one hour up to a few weeks.[1,2] The associated neurological symptoms can occur before, during or after the headache and have been reported to last from a few hours up to three days. The symptoms predominantly include sensory disturbance (78% of patients), aphasia (66%) and motor weakness (56%), usually on the opposite side to the hemicranial headache.[1] Visual disturbance is reported in 12% and is the least common neurological deficit. This is in contrast with classical migraine where visual symptoms are the commonest form of aura. Most people will have two episodes of neurological dysfunction, with complete resolution in between, but there are reports of up to 12 events occurring.[1,2]

The third key feature of this condition is a CSF lymphocytosis of 10-760 lymphocytic cells/mm^3.[1,2] CSF protein is often raised,[1,3] but oligoclonal bands are not detected. Elevated CSF opening pressures are also often found (up to 40 cmH2O), with resolution over time.[3]

The patient in this case report had all these characteristic features. An important part of the diagnostic process is early consideration of and, where necessary, exclusion of common infective, inflammatory and other potential causes for the clinical and CSF abnormalities (Box 2).[6] This is achieved by detailed clinical history taking, thorough neurological examination, repeat CSF and blood analyses and appropriate neuroimaging. Standard brain MRI is usually normal in HaNDL. However, there are some reports of abnormal neuroimaging findings such as hypoperfusion of clinically relevant areas on SPECT (single photon emission computerised tomography) and CT perfusion imaging and perfusion/ diffusion mismatch on MRI.[1,3,7] Catheter angiography is normal and has been reported to precipitate episodes of neurological symptoms.[3]

There is no specific treatment for HaNDL, the symptoms may be managed with migraine prophylactics such as propranolol (used in this case). Antimicrobial therapy, which may be started in the initial stages to cover for infective causes, should be stopped once key infections are excluded and a diagnosis of HaNDL is made. Symptoms should resolve within 3 months and no significant long term effects have been reported.[2]

Patients presenting to the emergency department with headache and focal neurological symptoms may go on to have a lumbar puncture for many reasons including exclusion of central nervous system infection or subarachnoid haemorrhage. If

Box 1. Diagnostic criteria of HaNDL as per The International Classification of Headache Disorders: 2nd Edition.[5]

- **A.** episodes of moderate or severe headache lasting hours before resolving fully and fulfilling criteria C and D;
- **B.** CSF pleocytosis with lymphocytic predominance (>15 cells/μl) and normal neuroimaging, CSF culture and other tests for aetiology;
- **C.** episodes of headache are accompanied by or shortly follow transient neurological deficits and commence in close temporal relation to the development of CSF pleocytosis;
- **D.** episodes of headache and neurological deficits recur over <3 months

Box 2. Key differential diagnoses for HaNDL syndrome to consider and exclude as appropriate

HaNDL syndrome - Differential Diagnosis

Infectious:
- Viral; HSV 1&2, VZV, HIV
- Bacterial; tuberculosis, syphilis, Lyme disease, mycoplasma
- Fungal; Cryptococcus

Immune mediated:
- Sarcoidosis
- SLE
- Antiphospholipid antibody syndrome
- Behcets
- ANCA positive vasculitis
- Primary CNS vasculitis

Neoplastic
- Primary CNS tumour
- Metastatic tumour
- Haematological malignancy (lymphoma, leukaemia)

the CSF shows a lymphocytosis and the headache has migrainous characteristics HaNDL syndrome is an important diagnosis to consider. However, care should be taken to exclude infective and inflammatory causes of a headache with CSF lymphocytosis. Overall, increased awareness of HaNDL syndrome in acute medical practice would be beneficial in minimising unnecessary invasive investigations and prolonged use of inappropriate antimicrobial agents which may cause adverse side effects.

Conflict of interest

Nothing to declare.

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