Case Report

Transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL-syndrome) with an acute confusional state and papilledema in a 10-year old girl: a case report.

Sietske Vermaning [a], Anna Jansen [b], Tim Vanderhasselt [c], Luc Régal [b], Tessa Wassenberg [b]

[a] Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussel, Belgium
[b] Paediatric Neurology Unit, Department of Paediatrics, UZ Brussel, Vrije Universiteit Brussel, Belgium
[c] Department of Paediatric Radiology, UZ Brussel, Vrije Universiteit Brussel, Belgium

sietskevermaning@hotmail.com

Keywords

Heachache, HaNDL syndrome, Pseudomigraine with pleocytosis, Cerebrospinal fluid lymphocytosis,

Abstract

The syndrome of transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL-syndrome) is a rare entity of unknown aetiology. We present a 10-year-old girl, with three episodes of HaNDL-syndrome, each characterized by slightly different neurological symptoms and signs. As HaNDL is a rare syndrome, a standardized therapeutic strategy has not been established. Treatment mainly consists of supportive therapy and in case of papilledema acetazolamide must be considered. We suspect that the diagnosis is often missed or mistaken for other neurological disorders.

Introduction

The syndrome of transient Headache and Neurological Deficits with cerebrospinal fluid Lymphocytosis (HaNDL-syndrome) is a rare entity mainly occurring in adults. However, it has been described in children as well (1,2). First described in 1981, it was initially referred to as migrainous syndrome with cerebrospinal fluid pleocytosis or pseudo-migraine with temporary neurological symptoms and lymphocytic pleocytosis (PMP-syndrome) (3). In 2018, the Classification Committee of The International Headache Society classified HaNDL-syndrome as a headache attributed to non-infectious inflammatory intracranial disease (4). HaNDL-syndrome is a self-limiting disease of unknown aetiology, which may relapse several times over a 3-month period. Diagnosis is made based on diagnostic criteria, which are listed in table 1.

We present a 10-year-old girl, with three episodes of HaNDL-syndrome, each characterized by slightly different neurological symptoms and signs. Recognition of this rare syndrome is important, because of its self-limiting character and favourable prognosis.

Case report (Figure 1, table 2)

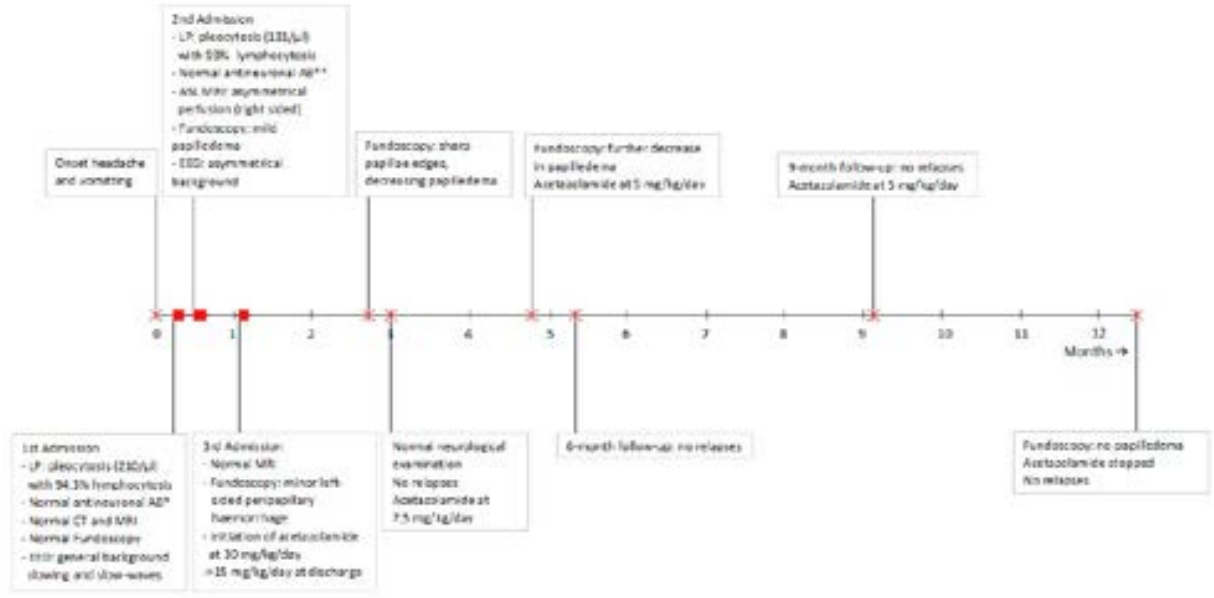
A 10-year old, previously well girl was admitted to our paediatric intensive care department. No history of recent febrile illness or recent vacation in (sub) tropical countries, and no chronic medication use. There were neither risk factors nor positive family history for strokes or migraines.

For one week, she had been complaining of bilateral frontal headaches and persistent vomiting, followed by a sudden change in consciousness. On presentation, she had stable vital signs and normal temperature. Neurological examination showed an apathetic girl with prosopagnosia and truncal ataxia, she was unable to sit and stand unaided. There were neither signs of lateralisation nor meningeal signs. Inflammatory parameters were negative in blood. Lumbar puncture revealed a pleocytosis (210/µl) with 94.3% lymphocytes. Empirical treatment with ceftriaxone and acyclovir was started intravenously and was stopped after 72 hours because of negative bacterial cultures and negative polymerase chain reaction (PCR)–based testing of common viruses and bacteria, including Herpes Simplex Virus. Borrelia and mycoplasma serology was

Table 1 Diagnostic criteria of HaNDL-syndrome according to the ICHD-3. (4)

A	Episodes of migraine-like headache fulfilling criteria B and C.
B	Both of the following:
	1. Accompanied or shortly preceded by the onset of at least one of the following transient neurological deficits lasting >4 hours.
	a) hemiparaesthesia b) dysphasia c) hemiparesis
	2. Associated with cerebrospinal fluid (CSF) lymphocytic pleocytosis (>15 white cells per µl), with negative aetiological studies.
C.	Evidence of causation demonstrated by either or both of the following:
	1. Headache and transient neurological deficits have developed or significantly worsened in temporal relation to the onset or worsening of the CSF lymphocytic pleocytosis, or led to its discovery.
	2. Headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF lymphocytic pleocytosis.
D.	Not better accounted for by another ICHD-3 diagnosis.

Figure 1. Timeline during HaNDL syndrome including follow-up. T=0 Onset of symptoms. Timeline is plotted with an interval of 1 month.



* Antineuronal antibodies included anti-Hu, anti-Ri, anti-Yo, anti-Ma2/TA, anti-CV2, anti-Tintin, anti-recoverin, anti-Sox1, anti-Zic-4, anti-GAD, anti-amphiphysin, anti-MAG, anti-AQP4 and anti-NMDA

** Antineuronal antibodies included anti-NMDA, anti-AMPA1/2, anti-CASPR2, anti-LGI1, anti-GABA-b, and anti-DPPX

negative. Anti-neuronal antibodies in cerebrospinal fluid (CSF) and serum were negative. Neuroimaging with computerized tomography (CT) scan and brain magnetic resonance imaging (MRI) showed no significant abnormalities. The electroencephalogram showed background slowing and slow-wave activities, suggestive for encephalopathy. Fundoscopy was normal. During the first hours of admission, she showed a progressive improvement, being more alert and responsive to questions and assignments. The first working hypothesis included cerebellitis or encephalitis of unknown origin. Electroencephalogram normalized during admission. She received supportive treatment with paracetamol, ibuprofen, and ondansetron. She fully recovered and was discharged after 5 days.

She was re-admitted 5 days after discharge, suffering this time from unilateral right-sided headache, continuous vomiting, unilateral left-sided numbness with paraesthesia and visual hallucinations. Neurological examination showed a somnolent but arousable child with brisk reflexes with a bilateral clonus on patellar reflex testing and pronation and lowering of the left forearm at the Barré test. Blood results showed no sign of infection and antinuclear antibody, antineutrophil cytoplasmic antibodies, sedimentation rate and rheumatoid factor were negative. Lumbar puncture showed pleocytosis (131/µl) with 93% lymphocytosis. Due to a technical difficult lumbar puncture, it was not possible to perform a pressure measurement. Cultures and PCR–based testing in CSF remained negative. Anti-neuronal antibodies in CSF and blood were negative. Electroencephalogram revealed an asymmetrical encephalopathic background pattern with slowing over the right cerebral hemisphere.

Arterial spin labelling (ASL) MRI brain perfusion revealed asymmetrical, lower perfusion on the right cerebral hemisphere, as illustrated in figure 2.

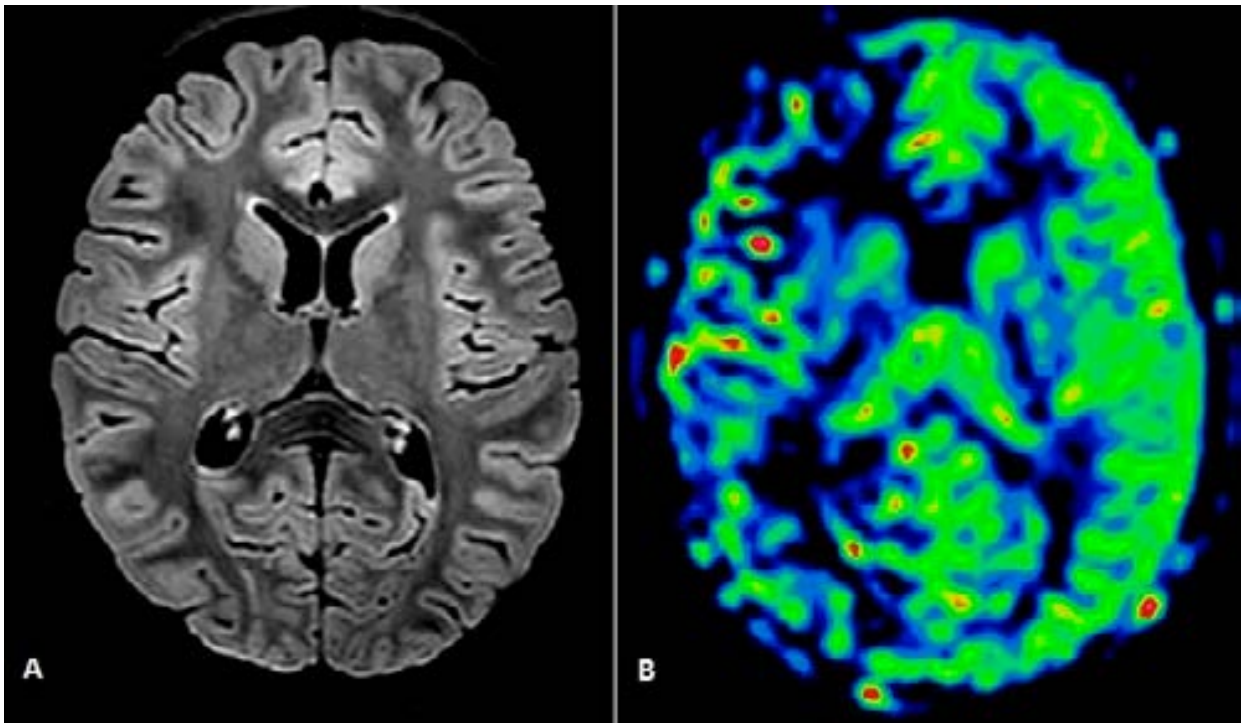
Bilateral mild papilledema was found on fundoscopy. Echocardiography was normal. Due to the recurrence of neurological symptoms and cerebrospinal fluid lymphocytic pleocytosis, HaNDL syndrome was put forward as differential diagnosis. Neither antibiotics nor antiviral treatment was started. She was hospitalized for 5 days with the same supportive treatment.

She had a third episode, 2 weeks after her second hospitalisation, starting with headache and vomiting, followed by aphasia. Parents described a short period of unilateral facial paralysis and opisthotonos. She was somnolent

Table 2 Performed tests to exclude infectious/inflammatory/autoimmune diseases, all tests turned out to be negative .

	Analysis performed and found all negative
Cerebrospinal fluid	Enterovirus, Herpes simplex virus type 1/2 (HSV), Varicella zoster virus (VZV), Human herpesvirus 6 (HHV-6), Cytomegalovirus (CMV), Human Parechovirus (HPeV), Escherichia coli K1, Epstein-Barr-virus (EBV), Mycoplasma pneumoniae, Haemophilus influenzae, Listeria monocytogenes, Neisseria meningitidis, Streptococcus agalactiae, Streptococcus pneumoniae, Cryptococcus neoformans/ gatti.
Serum	Paramyxovirus (parotitis epidemica) IgM, Rubella IgM, Adenovirus IgA, Human immunodeficiency virus type 1/2 (HIV), Varicella zoster virus (VZV), Herpes simplex virus type 1/2 (HSV), Borrelia burgdorferi IgG / IgM, Treponema pallidum, Mycoplasma pneumoniae Cytomegalovirus (CMV) IgG / IgM and Epstein-Barr-virus (EBV) IgG / IgM: Both immune and no current nor recent infection
Nasopharyngeal swab	Influenza A/B, Respiratory syncytial virus (RSV), Human parainfluenza viruses 1/2/3/4 (HPIV), Human metapneumovirus (hMPV), Chlamydia pneumoniae, Mycoplasma pneumoniae, Bocaparvovirus, Rhinovirus, Enterovirus, Adenovirus, Bordetella pertussis, Bordetella parapertussis Coronavirus type 229E / HKU1 / NL63 /AC43
Other serum tests	Antineutrophil cytoplasmic antibody (ANCA), Antinuclear antibody (ANA), Rheumatoid factor (RF)

Figure 2. Arterial spin labelling MRI perfusion.
A. Flair MRI
B. Arterial spin labelling at the same level showing decreased perfusion over in the right cerebral hemisphere.
Red and yellow colour means higher intensity, whereas blue means a low intensity.
No other abnormalities were seen on brain MRI



but arousable. Neurological examination showed brisk reflexes without clonus, disorientation in time and comprehension difficulties. A blood test showed mild leucocytosis with neutrophilia and negative C-reactive protein. Cerebral MRI was normal and fundoscopy showed mild bilateral papilledema with minor peripapillary haemorrhage in the left eye. Lumbar puncture was not performed. Supportive treatment was given together with acetazolamide (30 mg/kg/day, reduced to 15 mg/kg/d because of metabolic acidosis). She could be discharged after 4 days. There was a significant improvement in papilledema with acetazolamide treatment, which could be progressively tapered. At 6-month and 9-month follow-up, she did not show any recurrence of symptoms and was still taking a low dose of acetazolamide (5mg/kg/day). One year after initial presentation, she showed no relapses, papilledema had disappeared and acetazolamide was stopped.

Discussion

Our patient fulfils the diagnostic criteria of HaNDL syndrome according to third edition of the International Classification of Headache Disorders (ICHD-3) criteria, Table 1. HaNDL is a diagnosis of exclusion. Diagnosis of stroke, (hemiplegic) migraine, structural brain lesions, (mollaret) meningitis, (auto-immune) encephalitis, seizures, neuroborreliosis, neurosyphilis, neurobrucellosis, mycoplasma, granulomatous and neoplastic arachnoiditis and central nervous system vasculitis should be excluded (1,4). Episodes can last from 4 hours, up to 3 days. The transient neurological deficits can occur during or after headache onset. The syndrome resolves spontaneously within 3 months. Some patients (25%) have relapses, up to 20 episodes, during these 3 months (4,5). It is a self-limiting and benign syndrome. Between episodes, patients are asymptomatic. Intracranial hypertension with papilledema is described in several paediatric HaNDL cases, for which sometimes acetazolamide was initiated (1,2,4,9). HanDL syndrome is different from idiopathic intracranial hypertension in which no pleiocytosis is present, neurological examination is normal except for possible cranial nerve abnormalities, and clinical course is generally not benign.

The precise aetiology of HaNDL syndrome is not fully understood. The first hypothesis is based on a post-infectious and /or inflammatory mechanism as it is frequently associated (up to 33%) with a viral syndrome prior to signs of HaNDL syndrome (5,9). Infectious origins are systematically looked for but are almost always negative. There are some cases described where an infectious agent (HIV, CMV, *Borrelia lusitaniae*, HHV-6 and echovirus) was identified associated with or mimicking HaNDL syndrome (6,8,9).

Inflammation can be triggered by a viral infection, possibly creating a cortical spreading depression-like mechanism, which might cause the neurological symptoms and characteristics on EEG and cerebral perfusion MRI (9,11).

Others consider an auto-immune hypothesis, supported by a recent article, reporting antibodies against antibodies to a subunit of the T-type voltage-gated calcium channel CACNA1A in 2 patients with HaNDL syndrome (7).

The third hypothesis considers HaNDL-syndrome to be an atypical type of migraine, with longer symptom duration than classical migraine attacks and atypical aura (5). HaNDL syndrome shares some clinical features with hemiplegic migraine, including the duration of the attack and the possibility of hemiparesis. Were familial hemiplegic migraine can be linked with pathogenic variants in the *CACNA1A* gene, no variants were found in several patients with HaNDL syndrome (1). Most patients with HaNDL-syndrome do not have a personal or family history of migraine. Some patients suffer from migraine after HaNDL syndrome, favouring the migraine hypothesis (2). However, signs of intracranial hypertension and CSF abnormalities are not commonly associated with migraine, although not routinely investigated (9,10).

Several publications describe alternations in cerebral blood flow, as can be seen in migraine (11). Decreased blood flow is only seen during the acute phase (11). Most frequent EEG findings during the acute phase are slow delta or theta waves range (1,11). Our patient showed left-sided paraesthesia, right-sided decreased perfusion on cerebral MRI and right-sided background slowing on EEG during the second episode.

HaNDL syndrome is a rare entity in adults and sporadically (15%) occurs in children. To date, 30 children with signs compatible with HaNDL syndrome have been reported in the literature (9). In adults, peak age incidence is between 30-50 years. The youngest child reported was five years old. In adults with HaNDL syndrome there is no gender predominance, but in children seems to be a female predominance. HaNDL syndrome has a heterogenous aspect at (first) presentation, which makes it difficult to distinguish from other diagnoses. When relapses occur, a diagnosis of HaNDL syndrome becomes more likely. Neurological manifestations are sensory (78%), aphasia (66%), motor deficits (56%) and aura (18%), besides nausea/vomiting, weakness and decreased vision (5). In adults altered consciousness is rare, but in children it seems to be one of the possible clinical signs (2,5).

Given the benign character of HaNDL with its self-limiting nature, treatment is mostly supportive (1). While awaiting negative blood and CSF cultures and PCR results, antibiotic and antiviral treatment should be considered (2,3). In one case report (25-year-old patient), methylprednisolone was given, after which no more relapses occurred and the elevated intracranial pressure normalized. The positive effect of steroids in that case report supports the (post) infectious/auto-immune aetiology hypothesis (10). Patient education and reassurance about this syndrome is crucial during treatment and follow-up. Treatment consists of perfusion if necessary, antiemetics and pain-relieving medication. For patients with a clear diagnosis of HaNDL syndrome who present with a new episode within three months after onset, it may be reasonable to limit investigations including lumbar puncture. Fundoscopy can be valuable, as seen in our patient who developed papilledema resulting in a small peripapillary haemorrhage (4). Acetazolamide treatment should be considered, as raised intracranial pressure could give permanent visual sequelae when left untreated.

Conclusion

The syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis or HaNDL syndrome is a rare entity in children. It should be considered in children presenting with altered consciousness with lymphocytic pleocytosis and headache. It is a clinical diagnosis and the clinical picture can have different presentations in different patients. We suspect that the diagnosis is often missed or mistaken for other neurological disorders. The prognosis is favourable and considered benign, but one should remain aware of possible visual sequelae due to increased intracranial pressure.

Patient perspective

Given the unpredictable nature of this syndrome (unknown number of relapses, different neurological deficits each time), this created enormous psychological pressure and stress on parents and patient. The fact that it is a diagnosis of exclusion and waiting for some results could take several days, always raised the question whether all other diagnoses had been ruled out. After these three months, parents and school noticed that she was much more emotional and sensitive, cried easily and had mild concentration problems at school. Therefore, psychological follow-up was planned.

Informed consent

The patient and his family provided verbal consent to publish, and identifying information was excluded from the manuscript.

Disclosure of potential conflicts of interest: The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES:

1. Uptodate.com [internet]. Lay CL, Sun-Edelstein C. Syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL), Last updated 2019. Available from: https://www.uptodate.com.
2. Moavero R, Papetti L, Tarantino S, Battan B, Salfa I, Deodati, et al. Syndrome of Transient Headache and Neurologic Deficits With Cerebrospinal Fluid Lymphocitosis Should Be Considered in Children Presenting With Acute Confusional State. Headache. 2017; 58(3), 438–442.
3. Bartleson JD, Swanson JW, Whisnant JP. A migrainous syndrome with cerebrospinal fluid pleocytosis. Neurology. 1981(10); 31:1257-62
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1), 1–211.
5. Armiento R, Kornberg AJ. Altered conscious state as a presentation of the syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL syndrome) in a paediatric patient. J Paediatr Child Health. 2016; 52(7), 774–76.
6. Berthold O, Theophil M, von Moers A. HaNDL Syndrome with Fever in a 12-Year-Old Boy - A Case Report. Headache. 2018; 58(4), 597–98.
7. Kürtüncü M, Kaya D, Zuliani L, Erdag E, Içöz S, Ugurel E, et al. CACNA1H antibodies associated with headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL). Cephalalgia. 2013; 33(2):123-29.
8. Vieira JP, Brito MJ, de Carvalho IL. Borrelia lusitaniae Infection Mimicking Headache, Neurologic Deficits, and Cerebrospinal Fluid Lymphocytosis. J Child Neurol. 2019;34(12):748-50.
9. Armstrong-Javors A, Krishnamoorthy K. HaNDL Syndrome: Case Report and Literature Review. J Child Neurol. 2019;34(3):161-167.
10. Zhao L, Wang R, Fang H, Song B, Liang D, Xu Y. Chorea and the effectiveness of steroids in a patient with the syndrome of transient headache with neurologic deficits and cerebrospinal fluid lymphocytosis: a case report. J Pain Res. 2019;12:2247-50.
11. Fernández-Rodríguez P, Lojo-Ramírez JA, Medina Rodríguez M, Jiménez-Hoyuela García JM, García-Solís D. Differential diagnosis of HaNDL syndrome in a case report of a pediatric patient: The role of SPECT with 99mTc-HMPAO. eNeurologicalSci. 2020;19:100240.