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TITLE PAGE

Altered conscious state as a presentation of the syndrome of transient Headache and Neurological Deficits with CSF Lymphocytosis (HaNDL syndrome) in a paediatric patient

INSTRUCTIVE CASE

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MAIN TEXT

Abstract and Key Words

We describe the case of a previously well 12-year-old who presented with headache and rapidly progressive altered conscious state. After a period of intensive care support, she had rapid and complete resolution of her symptoms and HaNDL syndrome was diagnosed. HaNDL syndrome (the syndrome of transient Headache and Neurological Deficits with CSF Lymphocytosis) is a rare, benign and self-limiting condition. It is an important clinical entity to recognise as a diagnosis of exclusion.

Key words: HaNDL, Headache, Altered conscious state, Neurology

Text

Case Report

A previously healthy 12-year-old girl with a history of headaches presented with altered conscious state. She had had an upper respiratory tract infection 2 weeks prior to presentation. Onset was with 2 days of throbbing headache associated with blurred vision and vomiting. There was no associated fever and no infective features. On the day of presentation she reported a worsening headache and later became acutely confused, combative, had slurred speech and weakness which evolved over 1-2hrs. Her Glasgow Coma Scale (GCS) was 9 on arrival, and there was lower limb hypotonia and hyporeflexia. Plantar reflexes were equivocal and the remainder of her examination was normal. There was no evidence of meningeal irritation. Her conscious state deteriorated further and she was therefore intubated for airway protection. She received empiric IV Ceftriaxone and Aciclovir, as well as Dexamethasone for possible encephalitis.

CT brain was normal. MRI brain did not reveal any abnormalities on T1 or T2 weighted images, pre or post contrast images, diffusion weighted images or FLAIR images. MRI spine was also normal. Analysis of the cerebrospinal fluid (CSF) taken 24hrs after presentation revealed a lymphocytosis 48 $x10^6$/L, 0 polymorphs and a few red blood cells 3 $x10^6$/L. Protein was normal at 0.23 g/L (0.2-0.4) and glucose slightly raised at 4.2 mmol/L (0.2-0.4). An opening pressure was not obtained. CSF microbiological and virologic analyses including PCR for Enterovirus, Herpes Simplex Virus I and Adenovirus were negative. Normal investigations included liver function tests, electrolytes and renal function, thyroid function, ammonia, urine metabolic screen, creatine kinase, serum paracetamol level, blood and urine culture and viral PCR on nasopharyngeal aspirate. Other relevant investigations are listed in Table 1.

The patient was extubated after 24hrs and had a normal neurological examination thereafter. Aciclovir and Ceftriaxone were discontinued once CSF virology and microscopy, culture and sensitivity (MCS) were negative.

The patient had no further neurological events in the 4 months following the initial episode. A diagnosis of HANDL was made.

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Discussion

In the setting of headache and neurological dysfunction with aseptic CSF lymphocytosis and normal brain imaging, this patient fulfilled criteria for the syndrome of transient Headache and Neurological Deficits with CSF Lymphocytosis (HaNDL).

HaNDL syndrome is a rare, benign, self-limiting condition characterised by one or more episodes of transient neurological deficits associated with headache and CSF lymphocytosis[1]. Significant lymphocytosis is defined as >15 $x10^6/L$[1]. It was first described in 1981 and in 1995 Berg and Williams established the name HaNDL and provided diagnostic criteria[2-3]. Current diagnostic criteria are shown in Table 2. HaNDL syndrome has also been known as pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis, and as a migrainous syndrome with pleocytosis[1].

HaNDL is most commonly diagnosed in the third or fourth decades of life and is rare in the paediatric population[4]. Only 16 paediatric cases have previously been published[4-6]. A combative or altered conscious state is a rare neurological feature of HaNDL and only 9 cases have been reported, of which 1 was a paediatric patient[5,7].

Clinical presentation of HaNDL is with one to >20 episodes of moderate to severe headache associated with neurological deficits[1]. Neurological manifestations include sensory symptoms (78% of cases), aphasia (66%), motor deficits (56%) and less commonly aura-like visual disturbances (18%)[1]. There is a close temporal relationship between headache and neurological symptoms, which may occur before, during or after the onset of headache[8]. A viral infection precedes one third of cases, suggesting a possible aetiological link[5]. Symptoms usually resolve over hours but may persist for up to 3 days[1, 8]. Episodes may be isolated or if they recur, will do so in the first 3 months after the initial attack[1]. Patients are asymptomatic between events[1]. Thereafter, there are no further episodes and no neurological sequelae[8].

HaNDL is a diagnosis of exclusion, with the differential diagnoses including severe and life threatening conditions[1]. A leucocytosis may be present, though other blood tests are unremarkable[8]. There may be a raised opening pressure on CSF sampling (10-40cm H20)[1]. CSF shows a lymphocytosis (10-760cells/ml) and there is a high protein level in >90% (20-250mg/dl) with normal glucose and no oligoclonal bands. CSF culture and infective PCRs are negative. CSF lymphocytosis resolves over time, though the duration is unknown[4]. Routine CT and MRI brain must be normal[1]. Cerebral angiography is also normal[8]. Brain Single Photon Emission CT may show focal hypoperfusion in areas consistent with the clinical symptoms[6]. EEG shows focal slowing in the affected hemisphere, which is transient[5].

The pathophysiology of HaNDL syndrome is unknown[4]. There are three major hypotheses; firstly that it is a form of atypical migraine, though the duration of symptoms is longer than most migraines and the neurological features differ from a typical aura[8]. Most patients have no prior or family history of migraine[1]. Second is the suggestion of a meningoencephalopathy, though infective features are not present in all cases, and meningitic signs are absent[8]. The current leading hypothesis is neuronal spreading depression, likely triggered by viral infection, which triggers sterile inflammation[8].

Once diagnosed, management of HaNDL syndrome consists of symptomatic headache management[4]. Particularly given the potential for recurrent episodes within the first 3 months, education and reassurance of the patient and family is paramount[4].

This case highlights that HaNDL must be considered alongside more common differential diagnoses, even in the paediatric population, as a diagnosis of exclusion. Altered conscious state is a rare manifestation of HaNDL and this is the 2nd reported paediatric case[5]. Recognition of this diagnosis may prevent recurrent investigations that may be invasive or costly[4].

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Multiple Choice Questions

1. Which of the following is NOT a diagnostic criterion for HaNDL syndrome
a. Normal neuroimaging
b. CSF lymphocytosis
c. Ongoing neurological deficits >3months
d. Episodes fully resolve
e. Close temporal relationship between headache and neurological abnormalities

2. Which of the following is the most common neurological symptom
a. Sensory symptoms
b. Motor deficits
c. Altered conscious state
d. Visual disturbances
e. Aphasia

3. Which of the following investigations is NOT an associated feature of HaNDL syndrome?
a. Focal slowing on EEG
b. Raised CSF opening pressure
c. Raised CSF protein
d. Thrombocytopaenia
e. Normal cerebral angiography

MCQ Answers

1. c
2. a
3. d

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Tables

Table 1: Investigations	
Test	**Result**
Full Blood Examination	Mild neutrophilia 10.82 (1.8-8.0 x10^9/L)
C-Reactive Protein	<0.7 mg/L (<0.7)
Procalcitonin	<0.06 ug/L (<0.06)
Venous Blood Gas	Mild respiratory acidosis; pH 7.3, pCO2 50, HCO3 25, BE -2.4, Glucose 5.5
Urinary drug screen	Positive for Benzodiazepines and Opiates (after sedation)
Urine microscopy	0 leucocytes, 0 erythrocytes, no growth

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Table 2: International Headache Society (IHS) Diagnostic Criteria for HaNDL Syndrome[1]	
A	Episodes of moderate or severe headache lasting hours before fully resolving and fulfilling criteria C and D
B	Cerebrospinal fluid pleocytosis with lymphocytic predominance (15cells/ul) 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 <3months

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Key Points
1. HaNDL is a rare syndrome of transient neurological deficits accompanied by headache 2. HaNDL is a diagnosis of exclusion and may mimic severe or life threatening conditions 3. Altered conscious state is a rare manifestation of HaNDL

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