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BRIEF REPORT

Confusion as a presentation symptom of pseudomigraine with pleocytosis in a paediatric patient☆

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Received 23 April 2013; accepted 14 October 2013

KEYWORDS
Headache and neurologic deficits with CSF Lymphocytosis;
Pseudomigraine with pleocytosis;
Migraine;
Confusional syndrome;
Agitation;
Electroencephalogram

Abstract
Transient headache and neurological deficits with cerebrospinal fluid lymphocytic pleocytosis (HaNDL) syndrome is a rare condition of unknown origin that is characterized by episodes of severe headache, transient neurological deficits that recur over less than 3 months, and lymphocytic pleocytosis in CSF.
We report the case of a 14 year-old girl who presented with headache and vomiting that lasted 4 days, later combined with a clinical presentation of confusion, with a decrease in the level of consciousness, aphasia, peripheral facial paralysis, ataxia and fever for 24 hours. CSF analysis showed pleocytosis (110 cells/ml) and proteinorrachia (87 mg/dl). Electroencephalogram in the acute time showed generalized slowing, and later a focal slowing in the left hemisphere. She suffered 7 episodes of migraine (severe headache and vomiting) in the following two months, remaining asymptomatic thereafter.
This is the first paediatric case published in the literature that presents with an agitated and/or confused state. This condition must be considered in the differential diagnosis of patients with headache and acute altered level of consciousness, in order to avoid prolonged treatments or unnecessary invasive testing.

PALABRAS CLAVE
Cefalea con déficits neurológicos transitorios con pleocitosis linfocitaria;

Confusión como síntoma de presentación de una pseudomigraña con pleocitosis en un paciente pediátrico

Resumen
La cefalea con déficits neurológicos transitorios con pleocitosis linfocitaria en el líquido cefalorraquídeo (HaNDL) es una entidad poco frecuente y de etiología desconocida caracterizada por episodios de cefalea intensa, déficits neurológicos transitorios recurrentes durante 3 meses y pleocitosis linfocitaria.

☆ Please cite this article as: Soto-Insuga V, López-Villanueva L, Rodrigo M, Mois Aroyo I, Losada R, Soriano-Guillén L. Confusión como síntoma de presentación de una pseudomigraña con pleocitosis en un paciente pediátrico. An Pediatr (Barc). 2014;80:394-398.
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2341-2879/
http://dx.doi.org/10.1016/j.anpede.2013.10.004

Pseudomigraña con pleocitosis;
Migraña;
Estado confusional;
Agitación;
Electroencefalograma

Presentamos el caso de una niña de 14 años con cefalea y vómitos de 4 días de evolución, asociando posteriormente confusión, disminución de conciencia, afasia, paresia facial periférica, ataxia y febrícula durante 24 h. El análisis del LCR mostró pleocitosis (110 leucocitos/ml) y proteinorraquia (87 mg/dl). El electroencefalograma mostraba enlentecimiento generalizado en el momento agudo y posteriormente actividad lenta focalizada izquierda. En los siguientes 2 meses presentó 7 nuevos episodios de cefalea migrañosa permaneciendo asintomática después.
Es el primer caso pediátrico de HaNDL que se presenta como agitación y/o estado confusional. Esta entidad debe incluirse en el diagnóstico diferencial ante cuadros de cefalea y alteración de conciencia para evitar tratamientos prolongados o pruebas invasivas innecesarias.

Introduction

Headache and Neurological Deficits with CSF Lymphocytosis (HaNDL), also known as pseudomigraine with lymphocytic pleocytosis, is a neurological condition first described simultaneously by Swanson and Martí-Massó in 1980. While it is an infrequent condition, an increasing number of cases are being identified in the medical literature.[1] It is characterised by episodes of severe headache accompanied by transient neurological deficits and cerebrospinal fluid (CSF) pleocytosis over a period of less than 3 months. The patient is asymptomatic between episodes. The electroencephalogram (EEG) often shows non-epileptiform focal slowing. Conventional neuroimaging studies and other aetiological tests are usually normal. This condition is not rare in the paediatric age group[2,3]. Table 1 gives the diagnostic criteria for HaNDL as described by the International Classification of Headache Disorders (ICHD) in 2004.[4]

The associated neurological deficits are usually secondary to a cortical condition. The most common neurological manifestations are sensory symptoms (78%), aphasia (66%), motor symptoms (56%) and visual symptoms (18%).[5] Basilar territory symptoms are rare, found in only 6% of cases, usually with symptoms of vertigo, oculomotor disturbance, ataxia, and alteration of consciousness.[6]

Table 1 Diagnostic criteria.

A.	Episodes of moderate or severe headache lasting hours before resolving fully and fulfilling criteria C and D
B.	Cerebrospinal fluid 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

Diagnostic criteria of the *International Classification of Headache Disorders*, 21st edition, proposed by the International Headache Society (IHS).[3]

We present the case of a patient in which the main symptom of HaNDL was a confusional state.

Clinical case

Fourteen-year-old female with no prior history of headaches, with a maternal history of migraine, who sought emergency care in our centre with a 4-day history of clinical symptoms of severe headaches that limited her activities of daily living coupled with vomiting. The patient reported that in the last 4 hours, following a stressful life event, she had had decreased visual acuity in her left eye and a low-grade fever. On initial exploration she showed a confusional state (Glasgow Coma Score 11/15), agitation, and expressive aphasia accompanied by hypaesthesia in the right side of the body, right peripheral facial paresis, and ataxia (wide-based gait).

We did blood tests including a complete blood count, kidney function, ammonia, liver function, ionogram, glucose, and acute phase reactants, all of which were normal; as well as a urine toxicology screen, which was negative. The brain magnetic resonance imaging (MRI) did not show any lesions. We performed a lumbar puncture, which showed an opening pressure of 6 cm H_2O, 110 leukocytes/ml (85% mononuclear cells), a slightly elevated CSF protein level (87 mg/dl) with normal glucose levels, and negative oligoclonal bands.

She was admitted to our centre and initially treated with intravenous acyclovir (30 mg/kg/day) and intravenous ceftriaxone (80 mg/kg/day). We did serological tests for cytomegalovirus, Epstein Barr virus, herpes simplex virus 1 and 2, measles, mumps, *Rickettsia conorii*, *Brucella melitensis*, *Mycoplasma pneumoniae*, and *Borrelia burgdorferi*, as well as CSF bacterial cultures, and polymerase chain reaction (PRC) tests to detect herpes simplex virus 1 and 2, enterovirus, and antibodies for *Borrelia burgdorferi* in the CSF, all of which were negative. Antimicrobial therapy was therefore discontinued.

At 24 h the neurological deficits disappeared; the patient was afebrile from 36 h onward, and the headaches persisted until the seventh day.

We did another lumbar puncture on the sixth day, finding 250 leukocytes/ml (90% mononuclear cells), elevated glucose and protein level (152 mg/dl). The CSF pleocytosis decreased gradually; at 29 days a new lumbar puncture

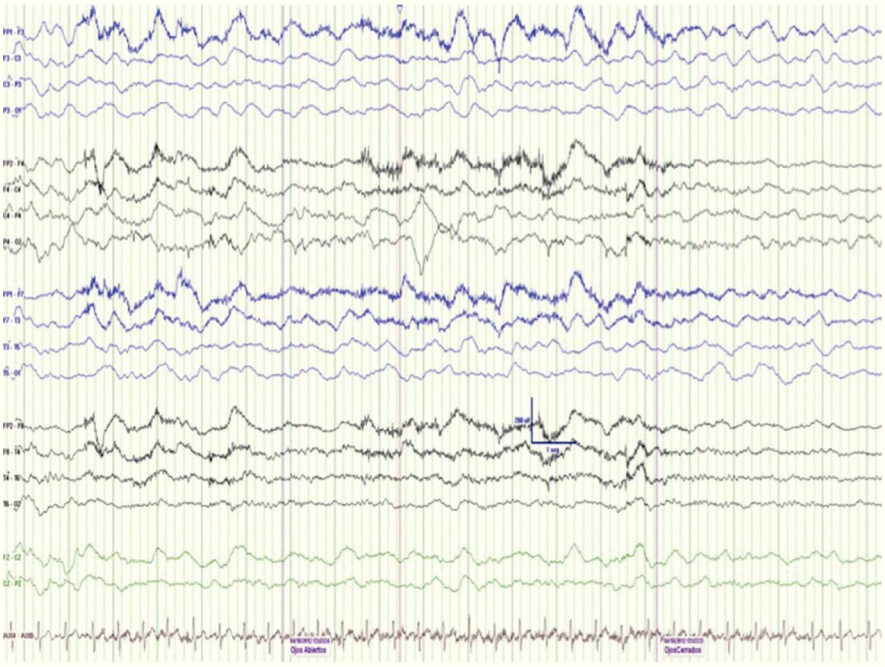

Figure 1 EEG during acute phase (day 1 of syndrome) showing generalised slowing.

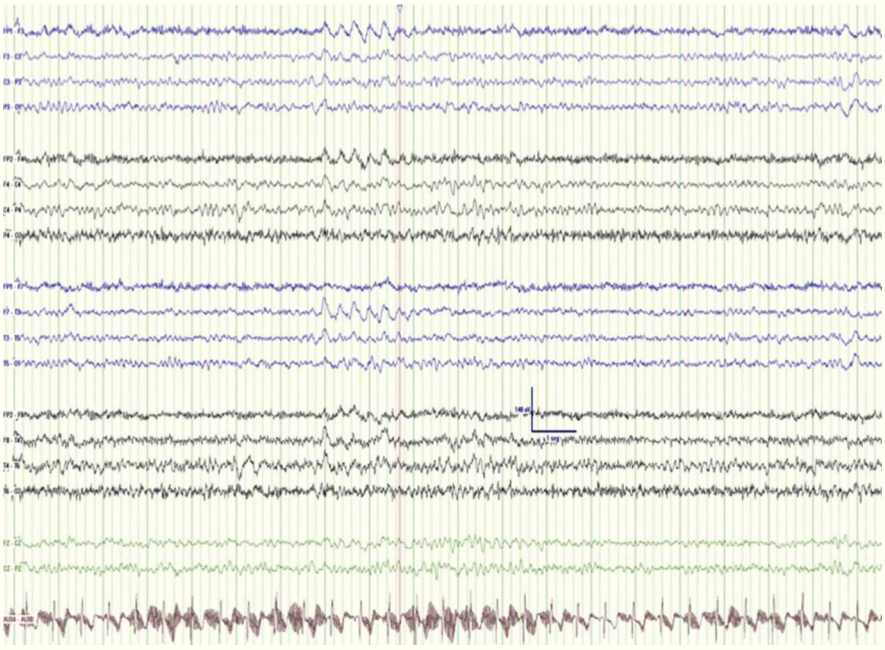

Figure 2 EEG during intercritical phase (day 22 of syndrome) showing localised left hemispheric slowing.

revealed 90 leukocytes/ml (90% mononuclear cells) with normal protein and glucose levels. We did another MRI with contrast at 7 days which showed no lesions.

A waking-state EEG was done while the patient had the neurological symptoms, in which we observed a generalised slowing of the background activity with no epileptiform features (Fig. 1). The electroencephalograms performed later at days 5, 22, and 36 showed slowing (delta wave bursts) localised in the left hemisphere (Fig. 2). The EEG tracing returned to normal at 3 months.

We started treatment with flunarizine (10 mg nightly) for 3 months, yet for two months the patient had 7 episodes of hypaesthesia on the right side of her body lasting 20 minutes each, followed by intense bitemporal throbbing

headache and nausea. The patient has not had new episodes of headache or neurological deficits since then (9 months follow-up).

Discussion

Our patient fulfilled the criteria for HaNDL described by the ICHD. Despite the latest published neuroimaging studies, which include images of transient hypoperfusion obtained by perfusion CT or MR during the acute phase of the syndrome, HaNDL remains a diagnosis of exclusion.[7,8]

Thus, when our patient presented with clinical symptoms of headache associated with confusion and agitation we had to make a differential diagnosis contemplating intoxication, metabolic disorders, meningoencephalitis, ischaemic disorders of the central nervous system, psychiatric disorders, as well as less common entities such as paraneoplastic encephalopathies, autoimmune encephalopathies, acute disseminated encephalomyelitis, non-convulsive status epilepticus, vasculitis, basilar migraine, and hemiplegic migraine. At first, we decided to treat the patient empirically with acyclovir and ceftriaxone suspecting a possible central nervous system infection by *Borrelia burgdorferi* or herpes simplex virus. Following the rapid resolution of neurological deficits, the negative results of an infectious work-up with the presence of CSF pleocytosis and focal abnormalities in the EEG led us to a HaNDL diagnosis, so we discontinued antimicrobial therapy.

Alteration of consciousness is a rare symptom in HaNDL, which complicates diagnosis even more in these cases. There have only been 8 prior descriptions of cases of patients presenting with confusion and/or agitation in the context of HaNDL syndrome.[9-13] This patient is the youngest of them; previously it had only been reported in adults.

The aetiology of HaNDL is unknown, and hypotheses have been proposed for infectious[14], vascular[15,16], and autoimmune causes, and for HaNDL being secondary to channelopathies.[17] At present, the most widely accepted hypothesis is that this process is secondary to an activation of the immune system due to an infectious/inflammatory process which in turns activates the trigeminovascular system, leading to the development of focal neurological symptoms by means of a mechanism similar to the neuronal spreading depression found in migraines with aura.[18]

The EEG at the acute phase of the syndrome showed a generalised slowing in the background tracing comparable to what is seen in other episodes of migraine with alteration of consciousness or familial hemiplegic migraine[19], which supports the possibility that HaNDL and migraine have a common physiopathology.[20] Subsequently, the EEG tracing showed the focal slowing characteristic of HaNDL until it returned to normal 3 months after the onset of the syndrome. None of the other HaNDL cases presenting with confusion symptoms previously reported in the literature described generalised abnormalities like those found in our patient, which was probably because the EEG were not done during the acute phase of the syndrome.

Although it is an infrequent condition, a HaNDL diagnosis in a patient presenting with headache and symptoms of confusion can prevent initiation of prolonged antimicrobial therapy or treatments with potential side-effects, such as thrombolytic drugs (for suspected ischaemic attack).

Conflicts of interest

The authors declare having no conflicts of interest.

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