Case report

Differential diagnosis of HaNDL syndrome in a case report of a pediatric patient: The role of SPECT with 99mTc-HMPAO

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1. Case report

We present a 14 years old girl without medical history who was treated at the hospital emergency services because of right foot paresthesias ascending to the entire ipsilateral hemibody gradually. Subsequently, those symptoms progressed to a deviation of the labial commissure, aphasia and acute confusional state. Furthermore, intense pulsatile hemicraneal headache was present. The patient was hemodynamically stable and there was no history of previous infection or fever. As the only medical background, she had developed milder symptoms like paresthesias and migraine-like headache two days before. The symptoms disappeared completely within 45 min mimicking a migraine with aura. The patient presented family history of migraine (mother and aunt). The patient did not obey orders, neither nominating nor repeating sentences during the neurological examination. Also, she presented a fluent but incoherent language and bilateral extensor plantar reflex. Neurological alterations were resolved spontaneously within 5 h. However, the patient was admitted for a neurological study.

A non-traumatic lumbar puncture was performed with clear fluid output and pressure at 260 mmH2O but papilloedema was no present. CSF revealed lymphocytic pleocytosis with a white blood cell count of 114 cel/mm³ (99% mononuclears), normal glucose (68 mg/dl) and protein (37 mg/dl) levels. Treatment with acyclovir was empirically started due to the presumptive diagnosis of encephalitis or viral meningitis. Serological analyses for other infectious diseases of central nervous system such as Lyme disease, neurosyphilis or neurobrucellosis were ruled out. Microbiological and virological analyses, including polymerase chain reaction (PCR) detection of varicella-zoster virus (VZV), herpes simplex virus (HSV) 1 and 2, enterovirus and Epstein Barr virus were also negative. Immunological analysis showed antineuronal, anticytoplasm and antinuclease antibodies negative.

An anti-NMDA antibodies test and a gynecological study to discard an ovarian teratoma were requested because of HaNDL syndrome that debuts with acute confusional state can mimic an anti-NMDA encephalitis [1,2]. Nevertheless, both studies were normal. T-type voltage-gated calcium channel antibodies were no demonstrated [3].

An urgent brain Computed Tomography (CT) and CT angiogram demonstrated no findings. An electroencephalogram (EEG) showed paroxysmal epileptiform waves in the left frontal (red-arrow) and left temporal region (blue-arrows) during hyperventilation (Fig. 1A). Five days after admission, the patient suffered from a third episode of right-sided hemiparesthesia with similar characteristics and migraine-like headache. A second lumbar puncture performed 3 days after that episode showed a CSF lymphocytosis (white blood cell count of 148/mm³) with normal protein and glucose content.

A control electroencephalogram in sleep-deprivation was performed presenting no significant alterations (Fig. 1B).

A brain Magnetic Resonance Imaging (MRI) showed no ischemic, hemorrhagic or space-occupying lesions. Pathological signal alterations in any sequence and restriction in the diffusion sequence were not present. No thickening of the arachnoid or duramater or pathological intra/extra-axial enhancements after contrast administration were
observed. Grey matter edema and sulcal enhancement were observed neither (Fig. 2A–C).

A Headache and Neurological Deficits with Cerebrospinal Fluid Lymphocytosis (HaNDL) syndrome was suspected due to a spontaneous recovery of neurological findings with negative etiological studies and normal imaging tests. Therefore, the patient was referred to the Nuclear Medicine Department to evaluate the cerebral perfusion. A brain perfusion Single Photon Emission Computed Tomography (SPECT) with $^{99m}$Tc-HMPAO (Hexamethyl propilen-amino-oxima) was performed five days after the last episode. It demonstrated significant decrease in blood flow of the entire left cerebral hemisphere in accordance with predominant right neurological symptoms. Those findings were consistent with the diagnosis of HaNDL Syndrome. In addition, a focal area of hypoperfusion was detected in the right anterior and medial temporal region. However, that finding was non-specific since it did not correspond to changes in the EEG or MRI (Fig. 2D–F).

Subsequently, a second $^{99m}$Tc-HMPAO brain SPECT was performed six weeks after the last episode, while the patient remained asymptomatic. The SPECT demonstrated a normalization of cerebral perfusion with complete reperfusion of blood-flow in the left cerebral hemisphere as well as in the right anterior and middle temporal region (Fig. 2G–I). The patient evolved favorably, and only received symptomatic treatment and lansosamide (anticonvulsant drug) because of disorders in the EEG. A control lumbar puncture was performed during the symptom-free period and showed a significant decrease in the number of cells (72 cells/mm$^3$) with persistence of normal protein and glucose levels. No relapses were noted in the follow-up period of one year and a half.

Fig. 1. A. Urgent electroencephalogram shows paroxysmal epileptiform waves in the left frontal (red-arrows) and left temporal region (blue-arrows) during hyperventilation. B. Electroencephalogram in sleep-deprivation without significant alterations. No paroxysmal activity, asymmetries or other encephalographic abnormalities are observed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
Meningitis is defined as meningeal inflammation. The main hypothesis of the etiology is an inflammatory process, characterized by pleocytosis ≥5 cells/mm³ in CSF, not related to an infectious process [8]. Aseptic meningitis is defined as meningeal inflammation accompanied by pleocytosis ≥5 cells/mm³ in CSF, not related to an infectious process should be considered in the differential diagnosis too. Up to two third of aseptic meningitis cases remain of unknown etiology. New entities have been described recently such as HaNDL syndrome which may decrease the proportion of idiopathic aseptic meningitis [10].

The most frequent recorded electroencephalographic findings during the acute attack are slow delta or theta waves ranges. The EEG tracing is normal in a high percentage of cases during intercritical periods [9]. Nevertheless, this case has verified epileptiform alterations in EEG could be detected in this syndrome. To our knowledge, HaNDL syndrome with epileptiform changes in EEG are very uncommon [11]. In this syndrome, normal brain imaging findings (CT or MRI) are characteristic. The absence of changes on diffusion-weighted MRI and asymmetrical decrease or increase in the blood flow velocity of the middle cerebral artery transcranial Doppler sonography during a HaNDL episode support a common pathophysiological denominator between migraine with aura and HaNDL syndrome [12,13].

Several publications have described alterations of cerebral blood flow found in the SPECT are congruent with focal neurological deficits [14]. In the majority of cases, there is a focal decrease in brain blood flow on the side of origin of the neurological deficits during the acute phase, although a decrease in cerebral perfusion has also been described throughout a hemisphere [9]. It was suggested that SPECT findings combined with EEG data, transcranial Doppler sonography and the clinical progression of neurological symptoms could be produced by a spreading depression-like mechanism similar to that proposed for migraine with aura [11].

Gomez-Aranda et al. described the first largest series of 50 patients who suffered from HaNDL syndrome and they included three patients in this series who underwent a brain SPECT revealing focal areas of hypoperfusion in accordance with clinical features with a progressive normalization of blood flow after recovery of the syndrome [15].

Camino et al. performed one of the first studies using a “dynamic” brain method (SPECT) to demonstrate brain alterations in four patients with HaNDL syndrome. They defined a local reduction of tracer uptake ipsilateral to the origin of the symptoms as well as the transitory perfusion defects in the same way as the clinical alterations that may remain for days or months. Moreover, this technique allows differentiating it from other entities such as the migraine with aura, in which focal perfusion defects in SPECT disappear at 24 h from the episode [16].

Other authors suggested, even in children with HaNDL syndrome, changes in cortical excitability and abnormalities in acetylcholine release as well as an electrophysiological pattern similar to that found in subtype of migraine with aura subtype but definite SFEMG abnormalities, increased IDAP and potentiation on PR-VEP [17]. However, this syndrome is not a migraine since patients do not meet the diagnostic criteria for migraine proposed in the International Headache Society...
classification [4].

In this case report, the patient presented an unusual EEG trace for the syndrome, with epileptiform waves in the left frontal and temporal regions. These features corresponded to areas of cortical hypoperfusion in the SPECT disappearing when the patient was symptoms-free. On the other hand, a focal area of decreased blood flow in the right anterior and medial temporal region was detected. From the point of view of the contralateral hemisphere. In this setting, a hypothesis could be that brain SPECT demonstrates other areas of cortical depression even in the absence of EEG or MRI changes. More studies are needed to understand how leptomeningeal inflammation with lymphocytosis in the CSF produces a spreading depression and secondarily, an oligemia with decreased cerebral blood flow in the SPECT associated with neurological symptoms.

HaNDL syndrome may be a condition probably underdiagnosed and seldom reported in pediatric age, so it should be taken into account as a differential diagnosis with migraine with aura, viral meningoencephalitis, transient ischemic attacks, epileptic seizures as well as aseptic meningoencephalitis in healthy children presenting recurrent headache and acute neurologic deficits. In the asymptomatic phase a comparative SPECT would allow to establish the self-limited nature of the disease by providing a potential role in the differential diagnostic and management of this syndrome [14].

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