Case report

ADENOVIRUS-INDUCED ACUTE NECROTIZING ENCEPHALOPATHY IN A PREVIOUSLY HEALTHY INFANT - A CASE REPORT

Carla Chikhani¹, Marwa Masri¹, Soha Ghanem², Ghassan Hmaimess³, Hicham Mansour⁴, Yolla Nassif¹, Dany Hamod⁵*

Author information: ¹ Department of Pediatrics, Saint Georges University Medical Center, Beirut, Lebanon, ² Infectious diseases, Department of Pediatrics, Saint Georges University Medical Center, Beirut, Lebanon, ³ Pediatric Neurology, Department of Pediatrics, Saint Georges University Medical Center, Beirut, Lebanon, ⁴ Neurometabolic Diseases, Department of Pediatrics, Saint Georges University Medical Center, Beirut, Lebanon, ⁵ Pediatrics and Neonatology, Department of Pediatrics, Saint Georges University Medical Center, Beirut, Lebanon.

Received: 04-02-2022; Accepted: 07-31-2023; Published: 08-22-2023

Abstract: Acute necrotizing encephalopathy of childhood has been described as a rare entity that usually affects immunocompetent infants and children, mainly in East Asia, and typically after a viral infection. We describe the case of an 8-month-old, previously healthy Lebanese boy, who presented with fever and seizures and was found to have acute necrotizing encephalopathy with Adenovirus detected in the CSF. The clinical presentation and laboratory and radiological findings are described, and the outcomes are discussed.

Keywords: Acute necrotizing encephalopathy of childhood (ANEC), Adenovirus, seizure, Lebanon, hyperammonemia, mitochondrial disease

INTRODUCTION Acute necrotizing encephalopathy of childhood (ANEC) was first reported in East Asian countries, mainly Taiwan and Japan. Its incidence in other parts of the world is infrequently reported. The clinical presentation and laboratory findings are not very specific. Therefore, clinical suspicion and radiological findings aid in establishing this diagnosis. The viral etiologies reported included mainly influenza virus, HHV6, and Human Parvovirus B19 [1-3]. The pathogenesis, however, remains unclear.

We describe here the case of an 8-month-old boy from Lebanon who was diagnosed with ANEC with associated Adenovirus detected in the cerebral spinal fluid (CSF).

CASE REPORT This is a case of an 8-month-old boy, born term by normal vaginal delivery with no perinatal complications, to non-consanguineous parents with no known medical history. The patient developed sudden twitching of the right eye followed by mouth deviation to the right and tonic clonic movements of the right upper and lower limbs. No vaccinations were done within 15 days of the event and the patient was up to date on all vaccinations including the pneumococcal vaccine.

The patient was admitted to the same outside institution 3 days prior to presentation. He was not easily aroused with a Glascow Coma Scale (GCS) of 7. Laboratory tests showed WBC 11,910/microL, neutrophils 63.2%, lymphocytes 25.4%, and C-reactive protein (CRP) 0.185mg/dL. Electrolytes, liver and kidney function tests were within normal limits. Investigations included blood, urine, and CSF cultures. Ceftriaxone at the meningeal dose and Acyclovir were started empirically after taking cultures. Acyclovir was discontinued after HSV 1 and 2 were not detected in CSF. Film Array for Meningitis/Encephalitis PCR panel was negative (E. coli K1, H. Infuenzae, L. Monocyctogenes, N. Meningitidis, S. Agalactiae, S. pneumonia, Cytomegalovirus, Enterovirus, HSV1, HSV2, HHV6, Human Parechovirus VZV, Cryptococcus neoformans, Cryptococcus gatti). CSF showed WBC 23/mm³, RBC 0, neutrophils 4% and lymphocytes 74%, glucose 58 mg/dL, Protein 0.2 g/L (Blood glucose 91 mg/dL, protein 61.9 g/L). Patient had

*Corresponding author: Dr Dany Hamod, Saint Georges University Medical Center, Ashrafieh, Beirut, Lebanon
Email: daalhamod@stgeorgehospital.org
Phone: +9613683209
recurrence of similar seizure episodes) for which he was started on valproic acid. Cat (CT) scan done prior to a lumbar puncture was normal and EEG showed slowing of the waves. An MRI showed the presence of areas of diffusion restriction in both lentiform nuclei, the left caudate, both cerebral peduncles in the midbrain, and ischemic/hypoxemic changes. Influenza A and B rapid tests were negative. Blood and urine cultures were negative.

The patient was then transferred to our hospital for continuation of care.

Initially, patient had a GCS 10 with normal bilateral pupillary reflexes, normal corneal reflex, no spasticity, normal Babinski reflex, and occasional spontaneous eye opening but no verbal responses. A meningeal dose of Vancomycin was added as empiric coverage prior to CSF culture results. Since the workup was inconclusive, Mycoplasma pneumonia serology was ordered. As part of the initial workup, the patient had hyperammonemia (125 microg/dL) for which he was started on sodium benzoate 100 mg/kg/day.

On day 2, CSF culture taken at presentation to the other hospital showed Acinetobacter Baumanii for which Meropenem was added and Ceftriaxone was stopped. An antiepileptic agent was switched from Valproic Acid to Levetiracetam to prevent drug interactions. The patient also had sudden clinical deterioration including desaturations and respiratory distress. GCS decreased to 6. The patient had flexion withdrawal to pain without eye-opening response or verbal response. Urgent intubation was done along with a repeat MRI of the brain that showed areas of restricted diffusion noted in both lentiform nuclei, the left caudate nucleus, the right occipital cortex, the right sensorimotor cortices, the right temporal lobe, and the midbrain with corresponding faint hypersignal intensities on fluid-attenuated inversion recovery (FLAIR) (Figure 1 and 2). The findings were suggestive of early subacute hypoxic ischemic brain injury. Since the patient had sudden clinical deterioration and the diagnosis of Acinetobacter infection was less likely, another CSF sample was taken for repeat analysis. Analysis of the CSF showed RBC 120/mm³, WBC 25/mm³, neutrophils 50%, lymphocytes 40%, monocytes 10%, glucose 58mg/dL, and proteins 47mg/dL. 16S rRNA sequencing along with a repeat viral panel (HSV1, HSV2, VZV, EBV, CMV, HHV-6, HHV-7, Adenovirus, Enterovirus, Parvovirus, Parechovirus) were ordered and turned out negative. Radiological findings, clinical status, and labs (hyperammonemia mainly) raised the possibility of an underlying metabolic disease (mainly a mitochondrial dysfunction), so the patient was also started on L-carnitine 100 mg/kg/day and coenzyme Q10 100 mg daily. Brucella serologies were also ordered since no other pathogen was identified and was negative.

During his stay, the patient started having bradycardia and hypotension for which he was started on dopamine and dobutamine, then eventually stopped. His cardiac ultrasound was normal.

On day 7, a viral PCR result showed that adenovirus was faintly detected so Cidofovir was administered to prevent further damage. Since HSV was not detected in the CSF, acyclovir was stopped. An EEG was also repeated and showed no changes from the first EEG with persistence in slowing of the waves. Given the clinical and radiological findings, acute necrotizing encephalopathy was suspected. A high dose of IV methylprednisolone was started (1g/1.73 m²) and given for 5 days. He was also started on Baclofen for increased spasticity.

A repeat MRI (Figure 3 and Figure 4) was done showing worsening T2 abnormal hyperintense signal and moderate enhancement involving mainly the putamen, internal capsules, external capsules and both cerebral peduncles. Scattered microhemorrhage foci were seen in the left cerebral peduncle and left cerebellar hemisphere. Antibiotics (Meropenem and Vancomycin) were stopped after a total of 10 days.

His GCS improved to 12 and the patient had spontaneous movements and spontaneous eye opening with grunting and agitation. He was weaned off mechanical ventilation and successfully extubated on Duo positive airway pressure (DuoPAP). His ammonia level was retested and was found to be within normal range, so sodium benzoate was discontinued. A second lumbar puncture was performed, and adenovirus was no longer detected after administration of Cidofovir. The first immunoglobulin therapy (IVIG) dose was given 2g/kg divided into 3 doses). The following two doses were given on day 21 and 22. Since the patient was clinically stable with very slow improvement in neurological status, he was discharged.
Figures 1 & 2. Restricted diffusion noted in both lentiform nuclei, the left caudate nucleus, right occipital cortex, right sensorimotor cortices, right temporal lobe, and midbrain with corresponding faint hypersignal intensities on FLAIR.

Figures 3 & 4. Worsening T2 abnormal hyperintense signal and moderate enhancement involving mainly the putamen, internal capsules, external capsules and both cerebral peduncles.
home after completing treatments of L-carnitine, coenzyme Q10, Baclofen, and Levetiracetam.

Three weeks after discharge, the patient was seen at the clinic and was found to have persistent peripheral spasticity, no eye fixation, and axial hypotonia. A few weeks later he developed infantile spasms (WEST syndrome) and was started on Vigabatrin, Clobazam, and Levetiracetam. During his last visit, 4 months after discharge, the patient was no longer having any spasms, and on physical exam the patient was awake, was able to fix and follow, did not have any peripheral spasticity, but still had a head lag.

DISCUSSION ANEC is a rare form of rapidly progressing encephalopathy and neurological deterioration in previously healthy children. It is most commonly identified in East Asia, but rarely in the Middle East. Nonetheless, case reports have been published about this entity in Saudi Arabia, UAE, Iran, and Egypt [4-7]. To our knowledge, this is the first case published about a Lebanese patient.

To identify this disease, Mizuguchi proposed five diagnostic criteria [8]:

1. An acute encephalopathy that follows a viral illness with a rapid decline in neurological status and convulsions.
2. Absence of CSF pleocytosis.
3. Multifocal lesions detected on brain CT scan or MRI, involving the bilateral thalami.
4. An increase in serum aminotransferases and no increase in ammonia level.
5. Exclusion of all other differential diagnoses.

The later, however, did not specify the minimum number of criteria needed for this diagnosis. The patient in this case met all the criteria except one (he had normal liver enzymes and an increased ammonia level). The hyperammonemia, however, resolved during his stay. Therefore, we raise the possibility of a secondary mitochondrial dysfunction causing the hyperammonemia and the basal ganglia lesions, which are often described in mitochondrial diseases, but not always in encephalitis. Another explanation would be the first unusual presentation of ANEC with hyperammonemia. A genetic and metabolic workup was requested from the parents but was later declined due to financial issues.

Many viruses have been associated with this entity, including Influenza A virus, HHV-6, and Parvovirus B19 that are either detected in serum or in CSF. Interestingly, the identified pathogen in our case was Adenovirus in CSF. A similar case was published in 2019 of a 14-month-old previously healthy girl in UAE who was found to have ANEC, but with adenovirus detected in her serum [7]. Adenovirus infection typically presents as gastroenteritis or conjunctivitis in previously healthy children and infants. However, the incidence of CNS infection and neurological involvement is rare [8]. There are approximately 51 serotypes of Adenovirus with serotype 7 most commonly identified in CNS infections and serotype 3 in encephalitis [7]. A systematic review done in Toronto in 2017 showed that the CNS involvement of adenovirus can range from a simple febrile seizure to meningitis, to severe encephalitis, and to acute necrotizing encephalopathy. It is stated in this study, nonetheless, that the detection of Adenovirus is rarely in the CNS, but most commonly in respiratory or gastrointestinal samples. An exception was noted, where Adenovirus was detected in CSF, however, the sample contained blood which could have altered the result. Most of the neurological sequelae were noted in children who were less than two years of age [8].

The radiological findings typical of ANEC include symmetrical multifocal lesions [9]. The involvement of the thalami bilaterally is imperative. Nonetheless, other parts of the brain may be involved. These include the upper brainstem tegmentum, the putamen, the internal capsule, the cerebral periventricular white matter, and the cerebellar medulla. The areas not involved were the optic nerve, subcortical white matter, pontine base, anterior part of the putamen, and spinal cord [10].

The treatment of ANEC remains controversial and is not well established. Antibiotics and antivirals are commonly initiated as clinical presentation can be very similar to meningitis or other diseases. After proper diagnosis, patients may be started on corticosteroids and IVIG. A retrospective study was done in Saudi Arabia on ANEC cases between 2015 and 2018. Intravenous methylprednisolone was administered to 83.3% of the cases, 30 mg/kg daily for 3 days, and intravenous immunoglobulin (IVIG), 1 g/kg daily for 2 days [5]. The early use of corticosteroids produced improved clinical outcomes [11] and the use of concurrent IVIG and
methylprednisolone improved survival rates significantly.[5] The use of Cidofovir in our case was targeted against the adenovirus in the CSF. The use of foscarnet, valganciclovir, or cidofovir has been recommended by some centers for disease control and prevention for immunodeficient children [12]. ANEC generally has a poor prognosis with high mortality and morbidity rates. Children are often left with severe neurological sequelae that are managed supportively. Early identification serves to improve the outcomes of ANEC patients [13].

CONCLUSION ANEC has been frequently described in children, commonly associated with certain types of viruses, most notably Influenza A virus, HHV-6, and Parvovirus B19, but rarely with Adenovirus. The early recognition of this entity, and its treatment aids in decreasing the associated morbidity and mortality. However, the above case might be a new presentation of ANEC with hyperammonemia or concomitant with a secondary mitochondrial disease.

REFERENCES
report. Indian J Child Health [Internet]. 2020 Jun 25 [cited 2023 Mar 8];07(06):280-2. doi:
10.32677/ijch.2020.v07.i06.010