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Case Report

Acute Necrotizing Encephalopathy in Children: A Case Report in Barranquilla-Colombia

Ricardo Andrés Sánchez Algarín[1], Angelica Maria Mendoza Caballero[1,*], Emanuel Alexis Troncoso Villadiego[1], Richard Romero Ruiz[2], Adolfo Álvarez Montañez[3]

[1]Pediatrics Department, Pediatric Specialized Care Center, Barranquilla, Colombia
[2]Pediatric Intensive Care Units, Specialized Care Center, Barranquilla, Colombia
[3]Pediatric Neurology Department, Pediatric Specialized Care Center, Barranquilla, Colombia

Abstract

Acute necrotizing encephalopathy is a rapidly progressive disease of the central nervous system that is generally described in texts as a pathology of pediatric patients, but even in people of this age range, it is rare to find a case of this disease, which presents with a fulminant tissue necrosis and can be secondary to infections, mainly of viral origin. Due to presenting very non-specific clinical manifestations, this diagnosis often goes unnoticed or is made late. ANE survivors go through three phases during the clinical course that include the prodromal stage, the period of acute encephalopathy, and the recovery stage. It is through specific radiological findings observed on computed tomography affecting the bilateral thalamus and possibly the cerebral white matter, brainstem, or cerebellum that the diagnosis can be confirmed. This report discusses the case of an 8-year-old schoolboy who begins with acute gastroenteritis, which progresses with seizures and neurological deterioration. A skull CT scan is performed with imaging findings suggestive of acute necrotizing encephalopathy. Management is established with adequate clinical response and favorable recovery of neurological symptoms. The clinical characteristics and radiological findings are the key to facilitating an early diagnosis, reducing sequelae and improving the prognosis, which provides a chance of life to people who suffer from this condition.

Keywords

Encephalopathy, Virus, Seizure, Neuroimaging

1. Introduction

Acute necrotizing encephalopathy (ANE) is a rapidly progressive disease of the central nervous system (CNS) [1], which causes fulminant tissue necrosis and can be secondary to infections, mainly of viral origin such as influenza A and B, herpes viruses 6 and 7, rubella, measles, respiratory syncytial virus, enterovirus, and even Sars Cov-2 [2], and Chikungunya [3] and other non-viral infections, such as Mycoplasma pneumoniae and the DPT vaccine. It was described as a clinicopathological entity for the first time in 1995 by Mizuguch et al [4] characterized by specific symptoms observed

*Corresponding author: angelicamendoza-19@hotmail.com (Angelica Maria Mendoza Caballero)

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on computed tomography as symmetrical multifocal brain lesions affecting the bilateral thalamus and possibly the cerebral white matter, brainstem or cerebellum [5]; Its incidence is unknown due to the variability of the clinical presentation and the difficulties in reaching a pathological diagnosis. The first reported cases were in the Asian continent (Japan, Taiwan and Korea); however, we currently find in the literature more than 300 cases globally, in North America, Europe, Saudi Arabia and sporadic cases in other countries [6]. A high morbidity has been described given the high risk of associated neurological deterioration that leads to a guarded prognosis during the course of the disease, only 10% of patients recover completely and the mortality rate is around 40% [7].

The case of an 8-year-old schoolboy who begins with acute gastroenteritis and progresses with neurological deterioration and imaging findings suggestive of acute necrotizing encephalopathy, with adequate response to established medical management; rare but important diagnosis to determine the evolution and prognosis of the disease.

2. Case Report

8-year-old male student, with no significant history, who consults first level of care for acute symptoms of 3 days of evolution consisting of unquantified thermal increases associated with low-output liquid stools managed with acetaminophen without achieving improvement, the condition progresses and the patient presents hypoactivity, hyporexia and the condition is exacerbated by presenting clonic movements in the left upper limb associated with fixed gaze, hypersalivation and trismus with a duration of approximately 3 minutes, with a postictal period of 10 minutes with repetition of seizures on 2 occasions. For this reason, he is referred to a more complex institution to carry out extension and evaluation studies for pediatric neurology.

At the physical examination on admission, the patient was found to be in fair general condition, feverish, disconnected from the environment, with a good respiratory pattern, no changes in abdominal semiology, good capillary refill, in terms of the neurological system, conscious, disoriented in time and space, uncooperative with examiner, aphasic, without meningeal signs, cranial nerves without alterations, deep tendon reflexes in the 4 extremities ++/++++, with positive bilateral Babinski, preserved tone, muscle strength 4/5 in the 4 extremities, Glasgow 13/15, ataxic gait and loss of support posture.

During stay in the pediatric intensive care unit (PICU), management is started with supplemental oxygen in case of crisis, antipyretic, intravenous fluids, impregnation with phenytoin (20 mg/kg/day) and maintenance (5 mg/kg/day), indicating midazolam (0.1mg/kg) in case of repeated attacks. They request studies (see Table 1) that report a complete blood count without cell abnormalities, negative PCR, arterial blood gases with compensated metabolic acidosis, preserved kidney function, normal calcium, ionogram with hypochloremic and mild hyponatremia. Imaging studies were performed with a chest x-ray report without alterations and a simple skull computed tomography (CT) that showed focal and symmetrical hypodensity at the bilateral thalamic level, without associated mass effect (See image 1).

A probable case of acute encephalitis of probable viral etiology is considered, a lumbar puncture is performed to study the cerebrospinal fluid (Cytochemistry, film array, gram and culture) and coverage with acyclovir is started (750 mg xm2 divided every 6 hours).

Six hours after admission to the PICU, he was evaluated by the neuropediatric service, who considered that the patient had neurological deterioration due to data of altered state of consciousness and tendency to drowsiness, few spontaneous movements, bradypsychia, and bradylalia. Therefore, an electroencephalogram and contrast-enhanced magnetic resonance imaging of the brain were requested and management was initiated with pulses of methylprednisolone (30 mg/kg/dose) for 5 days; Due to clinical suspicion of autoimmune encephalitis, an immunological profile is performed (C3, C4, ANA, ENA, ANCA); Since it was not possible to perform CSF filmarray (not available at the institution), it was consider necessary ruling out viral infection due to the patient's symptoms, therefore it was requested to perform IgE and IgM of varicella zoster - herpes virus 1, PCR for enterovirus, in CSF, in addition to anti NMDA in CSF and serum (see table 1).

Report of brain MRI with and without contrast: uptake and edema at the level of the thalamus, suspicion of acute necrotizing encephalitis, management with human immunoglobulin in continuous infusion of 8 hours is indicated.

Patient who, due to clinical and neuroimaging findings, is diagnosed with acute necrotizing encephalitis with direct involvement of the brain stem, after 5 days of established medical management, a good clinical response is evident, however, with persistence of motor neurological sequelae due to bradypsychia, bradylalia, impairment of gait, tremor in the right hand, memory and fine motor skills. After 1 week, it was decided to transfer to the hospitalization ward with oral corticosteroid with Prednisone 1 mg/kg as maintenance treatment.

Given the patient's improvement, discharge is considered by the pediatric neurology service after completing 15 days of hospital stay with outpatient evaluation by treating specialty, endocrinology, ophthalmology; requests brainstem auditory evoked potentials (BEATC) and visual evoked potentials (VEP), physical, occupational and speech therapy are indicated, as well as neurocognitive testing.

3. Discussion

ANE is a rare pathology that has been described mainly in the pediatric population, it predominantly affects children under five years of age [8], secondary to an infectious process in most cases of viral etiology, of a few days of non-specific symptoms with rapid progression and neurological deteriora-

tion, brain dysfunction, seizures and altered consciousness and even coma; In the study by Neilson et al [9], familiar or recurrent ANE was related to RANBP2 mutations in Europe and in the United States, and Sarigecili et al [10] showed that it can occur early or late in onset and can be recurrent and fatal, so early diagnosis and treatment are a fundamental pillar to impact the severity of this encephalopathy.

Regarding the pathogenesis, until now hypercytokinemia, known as the "cytokine storm" as explained by Kansagra SM [11], People who suffer from this pathology present an exaggerated immune response to viral infections and produce proinflammatory cytokines, with subsequent multisystemic compromise such as liver dysfunction, acute renal failure, shock and disseminated intravascular coagulation.

Laboratory findings vary from one case to another, mainly mild hyperproteinorrachia without pleocytosis and variable degrees of hepatic dysfunction without hyperammonemia, as well as in very few cases reported renal involvement.

Regarding the clinical manifestations ANE survivors go through three phases during the clinical course including the prodromal stage, the acute encephalopathy period, and the recovery stage. The diagnosis is made based on the clinical presentation and the characteristic multifocal brain lesions observed on computed tomography (CT), progressing from edema to petechial hemorrhage and then necrosis; regression or recovery from brain injuries is possible for survivors [12].

The absence of inflammatory cells in the brain parenchyma is characteristic, which differentiates this disease from the most common entities, such as acute disseminated encephalomyelitis and acute hemorrhagic encephalitis [13] and the neurological sequelae can be severe with motor, cognitive, auditory, and even visual impairment.

According to what was described above, hypercytokinemia occurs secondary to viral infections due to immune-mediated mechanisms, therefore immunomodulatory therapy, which blocks the production of cytokines, has shown good results to counteract the disease and improve the prognosis of affected patients. Intravenous glucocorticoids, immunoglobulins and plasmapheresis should be effective depending on the pathogenesis of ANE [14].

It is important to identify the risk and prognostic factors associated with this fulminant disease. For example, in a retrospective study conducted by En-Pei Lee et al, published this year; it was identified that ferritin may be a predictor of neurological outcome in patients with ANE, hyperferritinemia is associated with poor neurological outcomes and levels above 1823 ng/ml have an approximately eight-fold increased risk of poor neurological outcome [15].

Multiple cases have been reported in the literature, such as the one described by Said Saab et al [5] in the city of Barranquilla, in which acute necrotizing encephalopathy from childhood was diagnosed by imaging in a 4-year-old female patient, showing lesions of high signal in sequences with T1 and T2 information, rounded, well delimited at the level of the pons as well as involvement of the cerebellum in its medial portion, with good clinical response and satisfactory evolution of the disease.

However, not all of them have the same outcome as in the first case published in Costa Rica by Tautiva-Rojas [16], which deals with a 1 year and 3-month-old girl, with sudden neurological deterioration that required resuscitation and ventilation, who survived with significant morbidity such as neurological sequelae, tracheostomy and gastrostomy.

This work describes the course and clinical evolution of a patient with a rare pathology, but with easy diagnosis due to advances in neuroimaging, management with intravenous corticosteroid and immunoglobulins was established, which allowed an adequate response, currently presenting with motor neurological sequelae that will be treated on an outpatient basis with physical, occupational and neurocognitive therapy.

4. Conclusions

ANE is a pathology that should alarm us as pediatricians because it occurs mainly in children. It is also considered a high-morbidity condition that progresses rapidly, causing neurological deterioration and serious long-term sequelae. Therefore, recognizing the clinical characteristics and radiological findings are the key to facilitating early diagnosis and improved prognosis providing a chance at life for patients.

Abbreviations

ANE	Acute Necrotizing Encephalopathy
PICU	Pediatric Intensive Care Unit
CT	Computed Tomography
BEATC	Brainstem Auditory Evoked Potentials and Visual
VEP	Evoked Potentials

Author Contributions

Ricardo Andrés Sánchez Algarín: Data curation, Writing – original draft, Methodology.

Angelica Maria Mendoza Caballero: Conceptualization, Data curation, Project administration, writing – original draft, Writing – review & editing, Investigation

Emanuel Alexis TroncosoVilladiego: Investigation

Richard Romero Ruiz: Editing

Adolfo Álvarez Montañez: Supervision, Validation

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Conflicts of Interest

The authors declare no conflicts of interest.

Appendix

Table 1. *Evolution of paraclinics performed during stay in the ediatric Intensive Care Unit.*

STUDIES	INCOME 05/13/24	05/18/24	05/23/24
Hemogram	Leukocytes: 8,730 Hemoglobin: 14.2 Gr/dL Hematocrit: 42.61%	Leukocytes: 9,200 Hemoglobin: 13.9 Gr/dL Hematocrit: 41.72%	Leukocytes: 8,100 Hemoglobin: 13.8 Gr/dL Hematocrit: 40.32%
Sodium (mmol/L)	133.2	135.6	137
Potassium (mmol/L)	4.59	3.9	4.12
Chlorine (mmol/L)	9.5	10.1	9.6
Calcium (mmol/L)	1.77	1.56	1.87
Creatinine (mg/dL)	0.67	0.65	0.54
BUN (mg/dL)	9.81	6.81	10.4
Urea (mg/dL)	twenty-one	22	23
IgM	100		
IgG	889		
IgA	125		
ANA	Negative		
Varicella Zoster Antibody IgG-IgM	Negative		
GPT (UI/L)	10	13	12
GOT (UI/L)	twenty-one	28	25
C3	83		
C4	27.8		
Hepatitis B – Ag Surface	Negative		
Urinalysis + Gram	Not pathological		
Dengue IgM	Negative		
CSF cytochemistry	Color before centrifuging: (Colorless) Appearance before centrifuging: (Transparent) Color after centrifuging: (Colorless) Appearance after centrifuging: (Transparent) pH: (8.0) Density: (1.010) Glucose: (48) LDH: (81) Total Proteins: (99.1) Bacteria: (Not observed) Leukocytes: (Not observed) Bacteria: (Not observed) Yeasts: (Not observed) POLYMORPHONUCLEAR: (Absent)		
CSF culture	**Negative after 48 hours**		
PH	7,313	7.38	7,425
PCO2 (mmHg)	26.4	30.1	32.5
HCO3 (mmol/L)	16.9	19.3	22.1
B.E.	-6.9	-4.1	-23
PO2 (mmHg)	162	103	106
LDH (mg/dL)	476	352	248
CRP (mg/dL)	Minor 6	Minor 6	Minor 5

CSF culture	Negative after 48 hours
AC ANCAS	Negative
AC PANCAS	Negative
AC CANCA	Negative
ANTI SSB	Negative
ANTISM	Negative
ANTI RNP	Negative
ANTINUCLEAR ANTIBODIES	Negative
TOTAL EXTRACTABLE NUCLEAR ANTIBODIES	Negative
ENAS	Negative
ANTI RO	Negative
Electroencephalogram	Abnormal due to the inadequate organization of the background rhythms expected for age.
Brain Magnetic Resonance	Highly suggestive of hypoxic-ischemic lesions bilaterally and symmetrically involving the thalamus, inferior colliculi and vermis in the midline. Subtle changes of diffuse cortical cerebellar atrophy for the patient's age.

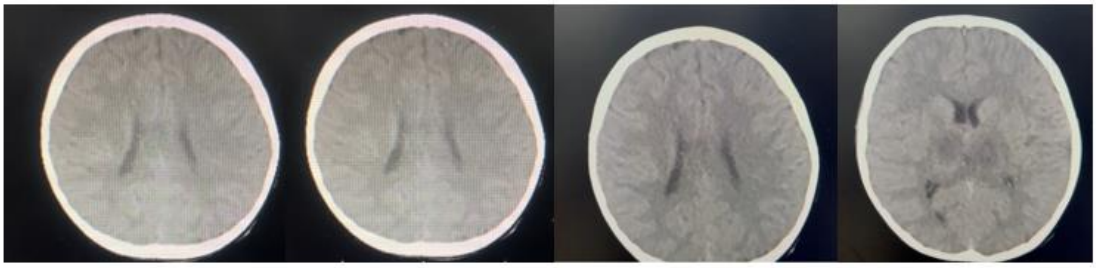

Figure 1. *Report simple skull computed tomography (CT): Axial cisterns of the base, Sylvians and grooves of the convexity without particularities. Ventricular system of preserved shape, size and position. Focal and symmetrical hypodensity at the bilateral thalamic level, without associated mass effect. No spontaneously visible intracranial blood collections are observed. Centered midline.*

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Biography

Angelica Maria Mendoza Caballero, doctor graduated from the Simón Bolivar University of Colombia, specialist in Pediatrics from the same institution and Master in clinical medicine from the University of Alcalá in Spain, currently taking the 2024 Boston Children's Global Pediatric Resident Digital Program and reviewer of American Journal of Pediatrics (AJP).

Ricardo Andrés Sanchez Algarín, general practitioner from Universidad Libre of Barranquilla, specialist in Epidemiology from Universidad Autonoma of Bucaramanga, currently a 2nd year resident of the Pediatrics Postgraduate Program at Universidad Simon Bolivar, and pursuing a diploma in pediatric and neonatal intensive care.