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Letters to the Editor

Acute necrotizing encephalopathy, a challenging diagnosis in a child with sudden neurological deterioration

María Tautiva-Rojas,[1] Sixto Bogantes-Ledezma[2]

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Abstract

Acute necroziting encephalopathy (ANE) is a rare and serious entity, with significant neurological involvement, in which the radiological findings of symmetric and multifocal necroziting lesions in central nervous system are characteristic. It is an immune-mediated disease with incompletely recognized pathogenesis. We present the case of a 1 year old child, previously healthy, that presented with acute neurological deterioration after a day of fever and seizures. She required reanimation and ventilation. Typical findings of ANE were found in neuroimaging and she was treated with inmunomodulating therapy, antibiotics and antivirals. Only rhinovirus and adenovirus were isolated in respiratory sample. The patient survived with significant neurological sequelae. This is the first case of ANE published in Costa Rica.

Keywords: Acute febrile encephalopathy, nervous system diseases, seizures

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Authors' affiliation:
[1]Hospital Nacional de Niños, San José, Costa Rica, Caja Costarricense de Seguro Social, San José, Costa Rica
0000-0001-5451-1963
[2] 0000-0002-7251-1278

Abbreviations: CCSS: Caja Costarricense del Seguro Social, ANE, Acute Necrotizing Encephalopathy; CSF, Cerebrospinal fluid, EM: emergency service, IVIG: intravenous immunoglobulin

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camila.tautivar@gmail.com

Acute necrotizing encephalopathy is a rare diagnosis, the prevalence of which is unknown, based mainly on characteristic radiological findings.[1] Initially it was considered to have a geographic predilection for the Asian continent, however, a global distribution has been described. It is associated with high morbidity, especially a poor neurological prognosis, and a mortality of up to 30%.[3,5] We present the case of a patient aged 1 year and 3 months, previously healthy, who after a day of irritability, respiratory symptoms, and fever, starts with seizures, sudden neurological deterioration, and severe encephalopathy. The diagnosis is made with the help of the radiologic characteristics described for this entity. Few cases have been reported worldwide and this is the first case to be published in Costa Rica.

Presentation of the case:

The patient is 1 year and 3 months old, with no known pathologies, with a history of the first consultation in a peripheral clinic for a day of irritability, fever, and dry cough that was managed as acute pharyngotonsillitis with oral antibiotics. She was reconsulted less than 12 hours later for a generalized tonic-clonic seizure and, not recovering her baseline neurological status, was transferred to the emergency department (SEM) of a third-level hospital of the Caja Costarricense de Seguro Social (CCSS).

On admission to SEM, the patient showed significant alteration of consciousness, unresponsive to the medium, and poor respiratory effort, in addition to evidence of shock and fever. The patient was initially intubated and placed on mechanical ventilation, and successfully resuscitated with fluids (saline solution at 50cc/kg), inotropic support (norepinephrine at 0.2mcg/kg/min), and an empirical antibiotic coverage was started (cefotaxime at 200mg/kg/d). Laboratory tests on admission showed pre-renal acute renal injury, alteration of coagulation times, slight elevation of transaminases, and elevation of inflammatory markers; in addition, a positive respiratory sample for *rhinovirus* and *adenovirus* was documented (see Table 1).

Table 1. Clinical laboratory results at admission

	Result	Normal range
Urea nitrogen	41.6 mg/dL	5-18 mg/dL
Creatinine	0.88 mg/dL	0.3-0.7 mg/dL
Sodium	142 mmol/L	138-145 mmol/L
Potassium	3.3 mmol/L	3.4-4.7 mmol/L
Aspartate aminotransferase	112 U/L	8-20 U/L
Alanine aminotransferase	59 U/L	7-35 U/L
Hemoglobin	12.7 g/dL	-
Hematocrit	38.3 %	-
Leukocytes	7,560 /uL	-
Platelets	292,000 /uL	-
Prothrombin time	18.7 sec	11-17 sec
Percentage of TP activity	59%	70-100%
INR	1.34	0.8-1.2
Partial thromboplastin time	30.1 sec	31-43 sec

During observation, the patient presented new seizures and remained encephalopathic, so a computed axial tomography of the brain was performed. The neuroimaging showed symmetrical hypodense lesions in both thalami, brain stem, cerebellar peduncles, midbrain, cerebellar hemispheres, and periventricular white matter (see figure 1). In addition, a cerebrospinal fluid (CSF) was obtained showing hyperproteinorrachia, without pleocytosis or hypoglycorrhachia (see Table 2). Due to persistent alteration of consciousness and suspicion of viral infection, acyclovir (30mg/kg/d) was added to the treatment.

Table 2. Cerebrospinal fluid results at admission

	Result	Normal range
Albumin	100 mg/dL	0-45 mg/dL
Glucose	81 mg/dL	60-80 mg/dL
Microproteins	156 mg/dL	15-45 mg/dL
Erythrocytes	10 mm3	-
Leukocytes	10 mm3	-
Bacterial culture	Negative	-
Film-array bio fire	No virus detection	-

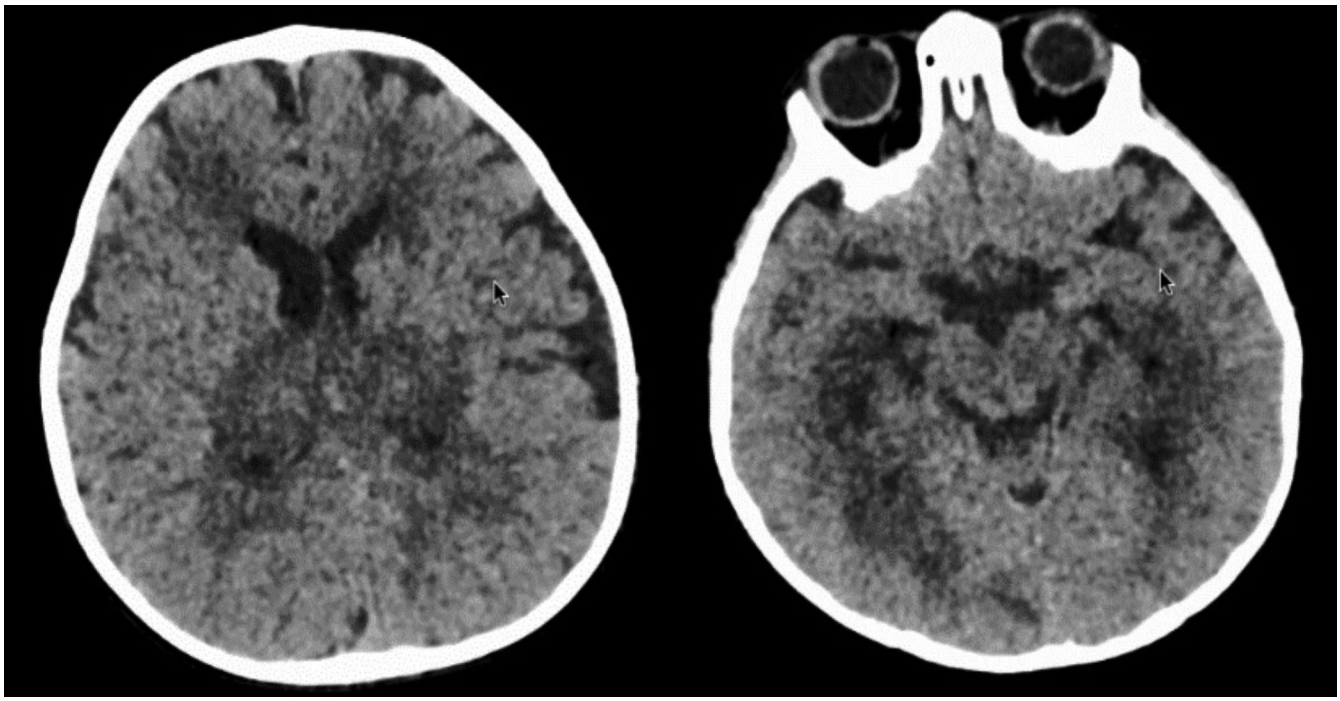

Figura 1. Computed axial tomography of the brain. Symmetrical hypodense lesions are observed in both thalami, brain stem and periventricular white matter.

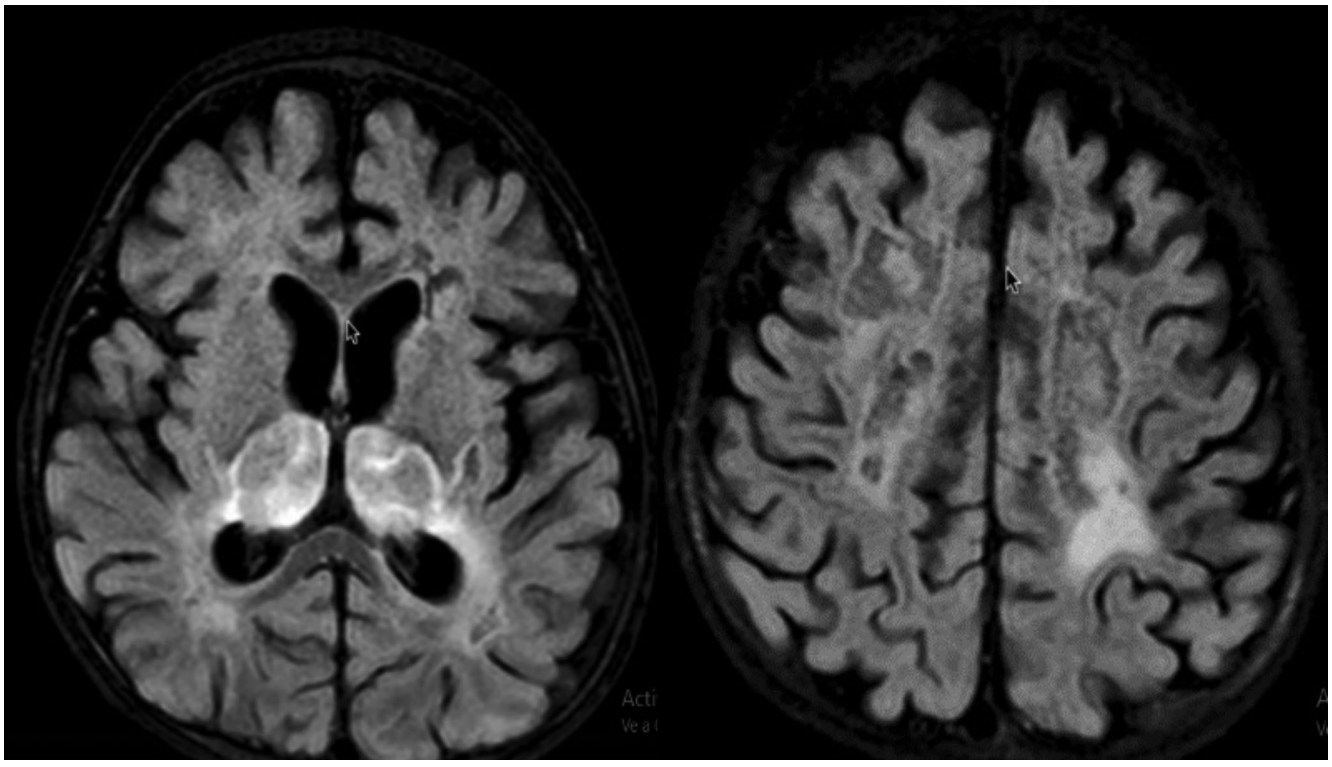

Figura 2. FLAIR brain MRI sequence. It shows hyperintensity in both thalami and uptake in white matter.

On day 2 of hospitalization, she was evaluated by a neurology specialist who, in view of the clinical evolution and imaging findings of the patient, established the diagnosis of acute necrotizing encephalitis (ANE) and started immunoglobulin intravenous immunoglobulin (IVIG) (2g/kg/d) immunomodulatory treatment. She was transferred to the intensive care unit where she persisted with neurological alteration and, in view of the severity criteria for ANE, methylprednisolone was added on day 3 of hospitalization. The patient presented relative improvement of her neurological status with greater response to stimulus but persisted with Axial hypotonia and limb hypertonus and was transferred to the general pediatric ward.

During hospitalization, she presented new convulsive crises with an electroencephalogram compatible with epileptic activity, so sodium valproate was added. Due to prolonged ventilation on day 10, she required a tracheostomy. On the other hand, due to neurological sequelae and data of swallowing dysfunction, surgical gastrostomy was performed, physiotherapy was started, and bromocriptine was added to the treatment. On the 21st day of hospitalization, a nuclear magnetic resonance was performed and documented diffuse volume loss and lesions in frontal, parietal, and bilateral temporal subcortical white matter; in addition to contrast-enhancing lesions in the cerebellum, pons tegmentum, midbrain, and almost all both thalami.

Completes a total of 7 days of cefotaxime, and 14 days of acyclovir, without isolating any bacterial microorganism at any time and without isolating any germ in CSF. In addition to 5 days of gamma globulin with methylprednisolone. She was discharged stable on day 35 of hospitalization after a multidisciplinary approach by pediatrics, nutrition, physiatry, physiotherapy, general surgery, pneumology, neurodevelopment, and neurology.

Discussion

Acute necrotizing encephalitis was initially described by Dr. Mizuguchi and his team in 1995 as a clinical entity in which symmetrical cerebral multifocal necrotic lesions are observed in the pediatric population, where the most characteristic feature is the neuroimaging findings.[1] It is a rare diagnosis, which makes it difficult to identify. In the case of our patient, the persistence of severe encephalopathy warranted a more exhaustive evaluation and assessment by specialists, which resulted in the diagnosis.

NAE is mainly described in the pediatric population, more so between 6 and 18 months of age, the age group to which our patient belongs. It usually presents with a prodrome of a few days of nonspecific symptoms with subsequent brain dysfunction, seizures, and altered consciousness with rapid onset of coma;[1] like what was observed in our case. Laboratory findings included alterations in different systems of which, compatible with what was reported, the patient had elevated inflammatory markers, prolonged coagulation times, elevated transaminases, and a CSF with hyperproteinemia and no pleocytosis.[1, 3]

To date, the exact pathophysiology of this entity is unknown, but it is proposed that there are individual susceptibility factors associated with environmental factors. [3,9] It has been mainly related to influenza virus and herpesvirus 6.[8] These patients present an exaggerated immune response to viral infections with an elevation of proinflammatory cytokines resulting in multiorgan dysfunction.[3,9] Brain injury occurs secondary to destruction of the blood-brain barrier with increased vascular permeability, cerebral edema, hemorrhage, and necrosis.[3]

In the case of our patient, 2 viral agents were isolated in respiratory samples, *rhinovirus,* and *adenovirus*, which could be the triggering cause of this process. No microorganisms were isolated at the CSF level, which is compatible with what is reported in the literature and supports the proposal that it is not a direct infectious pathology of the CNS.[1, 3, 5, 9] Sakrani et al. also report an *adenovirus-related* case of NAE; however, no *rhinovirus-related* cases are found in the literature.[4]

The topography of lesions at the cerebral level is very similar in all patients with NAE and includes the thalamus; typically bilateral, brain stem, white matter, and cerebellum.[3] Our patient presented with symmetrical lesions involving these structures, which were decisive in making the diagnosis and initiating treatment. However, she also had lesions at the cortical level in areas of marginal irrigation, which were not usually described in this pathology, probably related to the state of hypoperfusion in which the patient is received.

In 2015 Yamamoto et al. proposed a severity scale for NAE where 5 criteria are established and scored: shock on admission (3 points), more than 48 months (2 points), brain stem lesions (2 points), thrombocytopenia less than 100,000/uL (1 point) and hyperproteinorrachia greater than 60mg/dL (1 point). The risk is divided into low (0-1 point), medium (2-4 points), or high (5-9 points). [2] In our case, the patient is classified as high risk, which in the study by Lim et al. was identified as an important factor for subsequent neurological sequelae.[10]

There is no consensus in the literature on a standardized treatment for these patients, its dose or duration. [3, 5] The use of immunomodulators such as steroids, immunoglobulin, or plasmapheresis has been proposed, according to the pathophysiology, and a favorable response has been observed with them. [3] In addition, case reports have described therapeutic hypothermia as an option, considering its use to decrease cerebral edema. [11] Our patient was initially treated with intravenous immunoglobulin started within 24 hours of admission and, in addition, as she was classified as high-risk, systemic steroids were added to the treatment improving her neurological condition.

The literature describes that, despite treatment, these patients usually have a poor prognosis and a mortality of 30%.[3] In this case, although the patient survived, she presented significant neurological sequelae, which are within what is to be expected according to what is described for these cases.[10] Furthermore, apart from the severity of her initial presentation and the damage caused by the exaggerated inflammatory reaction, the hypoperfusion state in which she was initially treated may have contributed to the worsening of the lesions. The patient was discharged home and continues to be followed up by various specialties of the medical center.

The clinical characteristics and evolution, but mainly the CT findings, were decisive in making the diagnosis of NAE and initiating treatment. In the literature consulted *adenovirus-associated* cases are not frequently reported and there are no reports of *rhinovirus*, which were detected in our patient. In the absence of a consensus on TH the treatment of HUS, immunomodulatory therapy was provided to the improvement of the patient's neurological status, but with important sequelae.

References

1. Mizuguchi M, Abe J, Mikkaichi K, Noma S, Yoshida K, Yamanaka T, et al. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. J Neurol Neurosurg Psychiatry Res. 1995;58(5):555.

2. Yamamoto, H, Okumura, A, Natsume J, Kojima S, Mizuguchi M. A severity score for acute necrotizing encephalopathy. Brain Dev, 2005;37(3):322-327.

3. Wu X, Wu W, Pan W, Wu L, Liu K, Zhang H. Acute Necrotizing Encephalopathy: An Underrecognized Clinicoradiologic Disorder. Mediators Inflamm. 2015;(1):1-10.

4. Sakrani N, Almazrouei S, Mohan S, Ramsi, M. Adenovirus as a rare cause of acute necrotising encephalitis. BMJ Case Reports. 2019; 12. [posted 2019 Dec; cited 2021 Sep]: [3p.]. Available from: http://dx.doi.org/10.1136/bcr-2019-232338

5. Bergamino L, Capra V, Biancheri R, Rossi A, Tacchella A, Ambrosini L, *et al*. Immunomodulatory therapy in recurrent acute necrotizing encephalopathy ANE1: Is it useful? Brain Dev. 2012;34(5): 384-391.

6. Kansagra, S, Gallentine W. Cytokine Storm of Acute Necrotizing Encephalopathy. J Pediatr Neurol. 2011;45(6): 400-402.

7. Okumura A, Mizuguchi M, Kidokoro H, Tanaka M, Abe S, Hosoya M, *et al*. Outcome of acute necrotizing encephalopathy in relation to treatment with corticosteroids and gammaglobulin. Brain Dev. 2009;31(3): 221-227.

8. Suga K, Mori K. Fatal Acute Necrotizing Encephalopathy: Clinical Presentation and Imaging Findings. J Pediatr Neurol. 2015;53(1): 93-94.

9. Okumura A, Abe S, Kidokoro H, Mizuguchi M. Acute necrotizing encephalopathy: A comparison between influenza and non-influenza cases. J Microbiol Immunol Infect. 2009; 53(5): 277-280.

10. Lim H, Ho V, Lim T, Thomas T, Chan D. Serial outcomes in acute necrotising encephalopathy of childhood: A medium and long term study. Brain Dev, 2016;38(10): 928-936.

11. Vargas W, Merchant S, Solomon G. Favorable Outcomes in Acute Necrotizing Encephalopathy in a Child Treated with Hypothermia. J Pediatr. 2012; 46(6): 387-389.