Acute Necrotizing Encephalopathy: Case Report

Akut Nekrotizan Ensefalopati

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ABSTRACT Acute necrotizing encephalopathy (ANE) is a very rare disease in childhood. Most of the cases have been reported from far Eastern countries, and rarely from Western countries. The clinical course of ANE is rapidly progressive. The clinical features consist of hyperpyrexia, convulsions, recurrent vomiting and coma. Most of the patients die within a few days or result in severe neurological sequel. It is characterized with multifocal symmetrical and necrotic lesions in the central nervous system. We presented a 3 years 6 months old male with clinical and radiological findings of ANE in this case report.

Key Words: Leigh disease; magnetic resonance imaging; child; encephalitis

ÖZET Akut nekrotizan ensefalopati (ANE) çocukluk çağında nadir görülen bir hastalıktır. Batı ülkelerinden daha çok Uzak Doğu ülkelerinde görülür. Klinik seyri oldukça hızlı ve ilerleyicidir. Genellikle yüksek ateş, nöbet, tekrarlayan kusma atakları ve koma bulguları ile kendini gösterir. Olguların çoğu semptomların başlangıcından birkaç gün sonra ya ölümle ya da ciddi nörolojik sekelle sonuçlanır. Santral sinir sisteminde multifokal simetrik ve nekrotik lezyonlarla karakterizedir. Bu çalışmada, ANE tanısı alan 3.5 yaşındaki bir erkek olgu klinik ve radyolojik bulguları ile birlikte tartışılmıştır.

Anahtar Kelimeler: Leigh hastalığı; manyetik rezonans görüntüleme; çocuk; ensefalit

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Acute necrotizing encephalopathy (ANE) is a very rare disease, most commonly seen in childhood.[1,2] It is characterized with multifocal symmetrical and necrotic lesions in the central nervous system. Mainly in the thalamus, tegmentum, cerebellum, rarely in the internal capsule, posterolateral putamen and deep periventricular white matter.[1]

It occurs a few days after a febrile infection, together with vomiting, convulsions and coma. In childhood, its etiology is unknown; however, it's thought to be due to genetic and immune system dysfunction. Its prognosis is poor and less than 10% shows complete improvement. There is usually spasticity, mental retardation and recurrent convulsions.[1,2]

Oriental cases have been reported from Far Eastern countries, mainly Japan and Taiwan, and rarely from Western countries. Sporadic cases have been reported worldwide.[1-7] The reason for this preferential prevalence is unknown, but the disease is probably underdiagnosed and more frequent than suspected.[7] However, the clinical course of the disease is variable and frequently fulminant. In this report, we presented the clinical and radiologic findings of a living Turkish child with bilateral hemorrhagic thalamic necrosis due to ANE.

CASE REPORT

A 3 years and 6 months old male patient without any prior disease admitted with fever of ten days duration, cough, and nasal dripping. Despite oral amoxicillin-clavulanate treatment, the fever persisted. The child developed altered consciousness progressing vomiting and convulsions within the last 24 hours. He had not been immunized before the onset of signs. His family and personal medical history was not relevant. Pre-, peri-, and postnatal history was unremarkable. His psychomotor development was normal.

On physical examination, his general status was very bad, blood pressure was 120/60 mmHg, heart rate was 110/min, respiration rate was 28/min, and the body temperature was 38.4°C. His throat was slightly hyperemic. There were no abnormal findings in abdominal, cardiac and pulmonary examinations. Glasgow Coma Scale score was 9/15. Following the convulsions, his level of consciousness deteriorated, he became lethargic with increased tones in the whole body. Deep tendon reflexes were brisk and plantar reflexes were extensor. There was neck stiffness and papil edema in both eyes and the light reflexes were bilateral normal.

His laboratory data showed a white blood cell count of 29.500/mm^3 (in peripheral blood smear there were 85% neutrophiles, 15% lymphocytes), hemoglobin concentration of 11.9 g/dL, red blood cell count of 4.2 million/mm^3, platelet count of 327.000/mm^3, eritrocyte sedimentation rate of 30 mm/h, C-reactive protein of 4.93 mg/dL (normal < 5mg/L). Other remarkable biochemical tests revealed the following: alanine aminotransferase; 619 IU/L; aspartate aminotransferase; 421 IU/L. Prothrombin and partial thromboplastine time were normal. Arterial blood gas analysis and urinalysis were normal. Cerebrospinal fluid (CSF) analysis did not exhibit pleocytosis. Glucose in CSF was normal. The total protein value in CSF was elevated (138.6 mg/dL). The blood, urine and CSF culture remained sterile.

Cranial CT showed diffuse edema, suspicious increase of vascularity in the sulcus of convexities. Dexamethasone was given to patient for brain edema, also ceftriaxone and acyclovir. Cranial MRI revealed symmetrical lesions with low signal intensity at T1-weighted images at the level of thalamus (Figure 1); nearly homogeneous increment in pathological signals in upper brain stem, thalamus, splenium of corpus callosum and subcortical white matter at T2 weighted FLAIR images (Figure 2a ve 2b). The probable diagnoses were neuro metabolic disease and acute disseminated encephalomyelitis.

Tandem mass metabolic screening list was normal. Generalized tonic-clonic convulsions continued despite antiepileptic therapy phenytoin, phenobarbital and midazolam. EEG demonstrated, low intensity diffuse disorders of cerebral bioactiv-

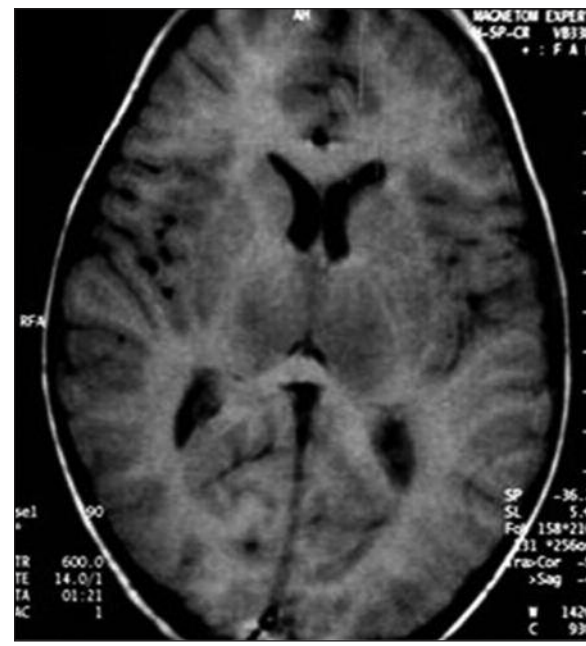
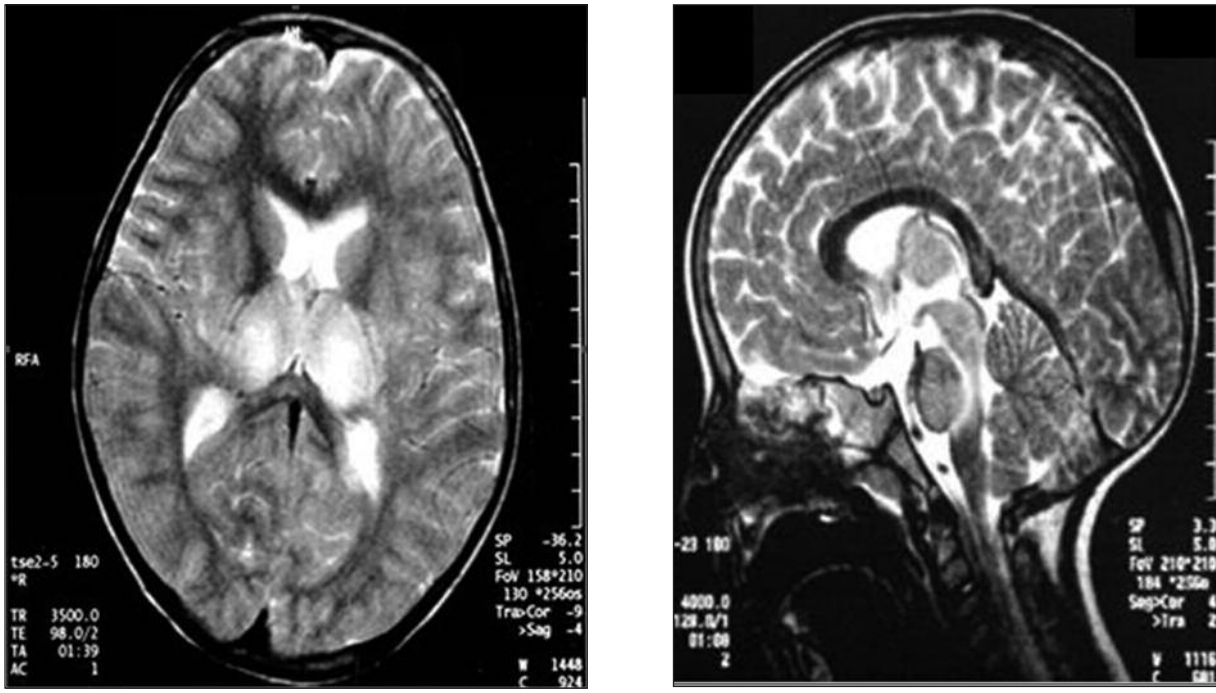


FIGURE 1: Axial T1 weighted MRI demonstrates symmetrical hypointense lesions at the level of thalamus with edema effect on the third ventricle.



a b

FIGURE 2a,b: Axial and sagittal T2 weighted MR images demonstrates pathological hyperintense lesions in upper brainstem, thalamus, splenium of corpus callosum with edema effect on the third ventricle and perimesencephalic cistern.

ity. The patient's clinical course deteriorated and on the eighth day of hospitalization cranial MRI showed hemorrhagic areas in thalamus and subcortical white matter in addition to the initially defined lesions and the axial FLAIR sections at the supraventricular level revealed, increase in the density of the lesion in white matter and a confluent appearance. Serology for influenza, cytomegalovirus (CMV), herpes simplex (HSV), herpes zoster, varicella (VZV), hepatitis, *Mycoplasma*, *Borrelia*, and leptospira produced negative results. Cultures and other laboratory investigations failed to reveal any causal agent. We planned to give intra venous immune globulin; however, as we could not obtain, we gave pulse steroids. Three weeks after admission the patient began to recover. On the forty-fifth day, the patient was discharged with spastic quadriparesis and mental deterioration and underwent a special physical and mental rehabilitation program. The child slowly recovered. His neurologic examination was notable for upper extremity weakness with minimal hand grip strength and 3/5 motor strength in the other muscle groups. Motor strength in the lower extremities remained 2/5. He was areflexic in the lower extremities with spasticity. He experienced persistent profound ataxia and speech difficulty.

DISCUSSION

Acute necrotizing encephalopathy is quite rare in child hood. It was initially described in 1995 by Mizuguchi as "childhood acute necrotizing encephalopathy".[1,4] Although its etiology is unknown; genetic, metabolic and immune disorders in childhood are thought to cause the disease.[3,5] There are case reports which suggest that HSV, VZV, CMV, EBV, hepatitis viruses, *Mycoplasma*, leptospira, Borrelia, HHV-6 and influenza A viruses might be playing role in etiology.[6] However, this disease is thought to be associated with cytokines, such as tumor necrosis factor receptor-1, interleukin (IL)-1, and IL-6.[8] In our case, all of the serologic tests were normal.

Acute necrotizing encephalopathy, generally occurs a few days after a febrile viral infection; its clinical course is characterized by vomiting, convulsions and coma.[1] Generally laboratory studies

show nonspecific findings like; elevated liver function tests, metabolic acidosis, elevated acute phase reactants and increased CSF protein.[2,7] The exact diagnosis depends on radiological and pathologic findings.[1,2,9] Radiological; there are multi focal, symmetrical and necrotic brain lesions in the thalamus, tegmentum, cerebellum, rarely in the internal capsule, posterolateral putamen and deep periventricular white matter.[1]

Differential diagnoses include, viral encephalitis, Reye syndrome, Wernicke encephalopathy, deep cerebral ven thrombosis, hypoxia, systemic lupus erythematosus, and some neurodegenerative disease (Leigh syndrome).[2] The neurometabolic disorders such as mitochondrial cytopathies, glutaric acidemia, methylmalonic acidemia, hemolytic uremic syndrome, and Wilson's disease are to be considered in differential diagnosis.[10] Leigh's syndrome, also known as subacute necrotizing encephalomyelopathy, is an uncommon inherited neurometabolic disease that affects the central nervous system and pediatric patients between the age of three months and two years. It is named after Denis Archibald Leigh who first described the disease in 1951.[11] In the case of the disease, mutations in mitochondrial DNA (mtDNA) or in nuclear DNA cause degradation of motor skills and eventually death. In addition, acute necrotizing encephalopathy affects mostly the thalami and none of these diseases is accompanied by symmetrical thalamic and other cerebral lesions seen in acute necrotizing encephalopathy.[10] Viral encephalitis can be differentiated from acute necrotizing encephalopathies by the presence of pleocytosis in CSF, while there are no necrotic lesions in toxic encephalopathies, other causes of encephalopathy are differentiated from acute necrotizing encephalopathies by their different locations of involvement.[12-14] Our patient admitted with fever of ten days duration, together with convulsions and unconsciousness. Laboratory studies showed leukocytosis, elevated liver function tests, metabolic acidosis and elevated acute phase reactants. Metabolic screening tests were normal. Cranial MRI showed pathologic findings compatible with acute disseminated encephalomyelitis.

The prognosis of ANE has been reported to be usually poor; approximately two-thirds of patients died or were discharged with severe neurologic sequel in previous reports. Early identification of risk factors predicting prognosis are important for quality assessment and appropriate treatment of the ANE. Recently, clinical and radiological prognostic factors of this disease have been studied.[8,10] For example, Wong et al[8] were assessed the outcome of each patient who diagnosed ANE according to 4 functions [The health state utility value (HSUV)]: 1. Physical function (mobility and physical activity), 2. Self-care and role activity, 3. Social and emotional function, and 4. Health problems (general health and disease status) with MRI findings. They reported that there was a significant and positive correlation between the clinical outcome and the MRI findings score, which was a composite of characteristic features including the presence of hemorrhage, cavitation, and location of lesions in ANE. In other reports, most authors have found that the younger than 2 years of age, those with high serum aminotransferase level, high protein levels of CSF, and reversible or symmetric brain involvement, focal neurologic signs are associated with poor prognosis of ANE.[8-10] There were elevated liver function tests, high protein levels of CSF, symmetric brain lesions of poor prognostic factors mentioned in our case.

The treatment modalities for acute disseminated encephalomyelitis include, pulse steroids, intra venous immune globulin, plasmapheresis, anti-viral and cytostatic drugs.[2,12] There is no certain consensus on the efficiency and choice of these treatment modalities. We believe that the effective use of early diagnosis methods such as MRI for ANE were most important factors for success of treatment.

As a result, we presented this case because it's rare in childhood, its prognosis is poor and it should be differentiated from other encephalopathies and neurometabolic diseases. Early differential diagnosis of such diseases may prevent neurological sequel and may provide a more favorable prognosis.

REFERENCES

1. Mizuguchi M. Acute necrotizing encephalopathy of childhood: a novel form of acute encephalopathy prevalent in Japan and Taiwan. Brain Dev 1997;19(2):81-92.
2. Ravid S, Topper L, Eviatar L. Acute necrotizing encephalopathy presenting as a basal ganglia syndrome. J Child Neurol 2001;16(6):461-2.
3. Renzo M, Franzoi M, Cogo P, Battistella PA. Acute necrotizing encephalopathy: combined therapy and favorable outcome in a new case. Child Nerv Syst 2006;22(10):1231-6.
4. Mizuguchi M, Hayashi M, Nakano I, Kuwashima M, Yoshida K, Nakai Y, et al. Concentric structure of thalamic lesions in acute necrotizing encephalopathy. Neuroradiology 2002;44(6):489-93.
5. Sazgar M, Robinson JL, Chan AK, Sinclair DB. Influenza B acute necrotizing encephalopathy: a case report and literature review. Pediatr Neurol 2003;28(5):396-9.
6. Wang HS, Huang SC. Acute necrotizing encephalopathy of childhood. Chang Gung Med J 2001;24(1):1-10.
7. Kim JH, Kim IO, Lim MK, Park MS, Choi CG, Kim HW, et al. Acute necrotizing encephalopathy in Korean infants and children: imaging findings and diverse clinical outcome. Korean J Radiol 2004;5(3):171-7.
8. Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH. Acute necrotizing encephalopathy of childhood: correlation of MR findings and clinical outcome. AJNR Am J Neuroradiol 2006;27(9):1919-23.
9. Malandrini A, Luchini D, Gambelli S, Gaudiano C, Berti G, Salvadori C, et al. A syndrome of bilateral hemorrhage of the thalamus and myocarditis with fatal course. J Clin Forensic Med 2004;11(4):208-10.
10. Seo HE, Hwang SK, Choe BH, Cho MH, Park SP, Kwon S. Clinical spectrum and prognostic factors of acute necrotizing encephalopathy in children. J Korean Med Sci 2010;25(3):449-53.
11. Noble P. Denis archibald leigh. Psychiatr Bull 1998;22(10):648-9.
12. Porto L, Lanferman H, Moller-Hartmann W, Jacobi G, Zanella F. Acute necrotizing encephalopathy of childhood after exanthema subitum outside Japan or Taiwan. Neuroradiology 1999;41(10):732-4.
13. Akarsu T. [Sudden unconsciousness and ADEM syndrome following upper respiratory tract infection: case report]. Turkiye Klinikleri J Pediatr 2010;19(3):234-8.
14. İdiman E. [Acute disseminated encephalomyelitis (ADEM)]. Turkiye Klinikleri J Int Med Sci 2006;2(28):65-8.