Childs Nerv Syst (2006) 22: 1231–1236
DOI 10.1007/s00381-006-0076-9

CASE-BASED UPDATE

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Acute necrotizing encephalopathy: combined therapy and favorable outcome in a new case

Received: 28 October 2005
Published online: 14 March 2006

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Abstract *Background:* Acute necrotizing encephalopathy (ANE) is a rare disease characterized by multiple, symmetrical brain lesions, affecting thalami, brainstem tegmentum, and cerebellar medulla; more inconstantly, other structures are involved, i.e., internal capsules, posterolateral putamen, and deep periventricular white matter. *Features:* The clinical picture consists of rapidly deteriorating acute monophasic encephalopathy preceded by prodromal febrile illness; the symptoms include hyperpyrexia, convulsions, recurrent vomiting, and coma within 24 h. *Prognosis:* The outcome is usually poor and approximately 70% of the patients die within a few days from the onset of fever. There is no specific therapy for ANE but, in some patients, the clinical status improved with steroid treatment.

Keywords Acute necrotizing encephalopathy · ANE · Acute encephalopathy · Magnetic resonance imaging · Infants and children

Background

Introduction

Acute necrotizing encephalopathy (ANE) is a rare disease firstly described by Mizuguchi et al. [15], which affects young children in the Far East countries, mainly Japan and Taiwan [14, 22], and recently also in the North America and Europe [3, 12, 19–21, 23]. It is characterized by multiple, symmetrical brain lesions, affecting bilaterally the thalami, brainstem tegmentum, and cerebellar medulla [15]. The clinical picture consists of rapidly deteriorating encephalopathy preceded by prodromal febrile illness after an interval of 1 to 3 days. The symptoms include hyperpyrexia, convulsions, recurrent vomiting, and coma within 24 h [15]. Approximately 70% of the patients die within a few days from the onset of fever [14]; but, recently, a wider spectrum of disease severity was demonstrated, with cases exhibiting milder symptoms and good outcome [10–12, 14, 25]. A recent review reported 92 cases published in literature [10].

Clinical features and diagnosis

Clinical presentation shows rapidly evolving symptoms including decerebrate or decorticate posture, deep tendon hypereflexia, Babinski sign and inconstant miosis and papilledema. Meningeal signs, abnormal involuntary movements, and focal neurological signs are usually absent.

In early phase of ANE, laboratory findings often show hematological changes resembling disseminate intravascular coagulation, i.e., decreased fibrinogen, thrombocytopenia, and elevated serum glutamic–oxaloacetic transaminase (GOT) and glutamic–pyruvic transaminase. Moreover, it is possible to find increased urea and creatine kinase, metabolic acidosis, hypoproteinemia, increased levels of C-reactive protein, and higher erythrocyte sedimentation rate [10, 21]. These findings, however, were absent in the case described here. Cerebrospinal fluid (CSF) usually shows high pressure and increased amount of protein.

Pathogenesis

The hallmark of this encephalopathy consists of multifocal symmetrical necrotic brain lesions affecting both thalami, upper brainstem tegmentum, and cerebellar medulla [15]. Other structures are more inconstantly involved, i.e., internal capsules, posterolateral putamen, and deep periventricular white matter [3, 8, 10, 13].

The pathogenesis of ANE in childhood is still unknown but is thought to be due to an immune-mediated mecha-

nism [20]. The high incidence of ANE in Japan and Taiwan suggests the involvement of genetic or epigenetic factors [21]. The basis for the characteristic selective vulnerability of the thalamus, brainstem, and cerebellum remains obscure.

Diagnostic investigations

Radiology

Brain computed tomography (CT) findings of ANE consist in symmetrical areas of low attenuation in almost the whole thalami, pontine tegmenta, and cerebellum [15]. However, CT images may not show lesions in the very early phase of ANE [24]. Magnetic resonance imaging (MRI) shows abnormalities in the same areas as disclosed by CT, characterized by prolonged T_2 and T_1 relaxation times; contrast-enhanced T_1-weighted images show mild enhancement mainly in the margin of the thalami and, in some cases, around the pontine tegmenta and the deep cerebral and cerebellar white matter [1, 14, 16].

Diffusion-weighted MRI [1, 14], as well as proton MR spectroscopy [6], recently resulted effective in predicting neuropathological and clinical outcome in acute phase of ANE.

After a first few weeks, if the patient survives, the areas of abnormal signal intensity become more demarcated and smaller in thalami and totally resolved in pontine tegmentum and cerebellum [24], as it happened in the case illustrated below.

Histology

A necropsy examination of some patients affected by ANE shows extensive fresh necrosis of the regions detected by neuroimaging, i.e., thalamus, pontine tegmentum, and cerebellar medullary substance bilaterally with evidence of local breakdown of the blood–brain barrier, but without necrosis of blood vessels [15, 16, 24]. In particular, a microscopic examination of brain shows necrosis of neurons and glial cells and frequent petechiae in the thalami, without proliferation of reactive astrocytes or microglial cells. Furthermore, there is loss of axons and extravasation of erytrocytes in the central lesions [24].

Differential diagnosis

From the clinical pathological and radiological features, ANE should be differentiated from other acute disorders characterized by bilateral lesions in the cerebral deep gray matter, including mitochondrial encephalopathies, organic acidemias, and carbon monoxide poisoning.

Acute disseminated encephalomyelitis (ADEM) is an acutely post-infectious/post-vaccinal inflammatory demyelinating disease, characterized by multifocal, sometimes confluent, areas of perivenous inflammation accompanied by demyelination of the deep white matter of the brain, including basal ganglia, brainstem, and spinal cord. Kumada et al. [11] reported an infant affected by ADEM with CT lesions similar to those of ANE. Harada et al. [7] more recently briefly described diffusion-weighted images of an ANE patient comparing these two different kinds of encephalopathy. Decreased apparent diffusion coefficient (i.e., cytotoxic edema) was evident in an ANE patient, while ADEM lesions exhibit vasogenic edema, suggesting different pathogenetic mechanisms. This hypothesis seems to be confirmed by the different time course of ANE vs ADEM after a prodromal illness, i.e., usually 2–4 days for ANE compared with 2–3 weeks for ADEM. Other authors conclude that diffusion-weighted imaging findings correlate well with neuropathologic data and, during the acute phase of ANE, that it may also be effective in predicting both the degree of neural destruction and neuromotor skill [1].

The "fulminant" form of ADEM is described by Weston Hurst [9] as acute hemorrhagic leukoencephalitis, characterized by asymmetric widespread involvement of the white matter of the brain, with larger, more confluent lesions associated with more edema and mass effect. There are pathologically perivascular and ball hemorrhages, serious exudates, perivascular neutrophilic leukocytic infiltrates, foci of demyelination, degeneration of small blood vessels with fibrinoid replacement, and glial nodules [5].

The differentiation of ANE from viral encephalitis is based on CSF analysis, as in the last condition CSF pleocytosis is common. In acute toxic encephalopathies, necrotic lesions are not described. Acute bilateral thalamic necrosis has been also described in *Mycoplasma pneumoniae* infection [2].

Leigh syndrome differs by its neurodegenerative course, persistent lactic acidosis, and other sites of disease localization, besides basal ganglia such as periaqueductal grey, optic nerves, inferior olive and spinal cord, not involved in ANE [4].

Wernicke encephalopathy, caused by thiamine deficiency, shows lesions in the thalamus and mamillary bodies.

Autosomal dominant acute necrotizing encephalopathy represents an autosomal dominant acute necrotizing encephalopathy with a clinical pattern similar to ANE and MRI lesions distributed primarily in the thalamus and brainstem after a febrile illness. Oxidative phosphorylation of intact mithocondria from a muscle biopsy shows loose coupling [18].

Reye syndrome is an acute encephalopathy associated with fatty degeneration of the liver and metabolic changes such as hyperammonemia and hypoglycemia. Brain imaging in Reye syndrome generally shows diffuse brain edema with only patchy, if any, necrosis, unlike the widespread

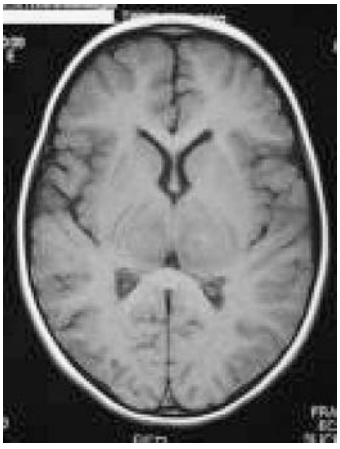

Fig. 1 A CT scan performed on hospital admission during the early acute phase of illness shows hypodense lesions in both thalami

symmetric necrosis of ANE [14]. Other possible causes of thalamic involvement include thalamic infarction and deep cerebral vein thrombosis.

Prognosis

Despite treatment, death occurs in a large proportion of patients affected by ANE. In surviving cases, the recovery of consciousness begins between the sixth to the tenth day and improvement of neurological functions continues for several months [15]. Less than 10% of patients recover completely and most patients show variable neurological sequelae: spasticity, mental retardation, and epileptic seizures [25]. Cognitive functions, however, show good recovery compared with motor signs [15].

Prognosis is better in older children and in cases with asymmetric thalamic involvement, low GOT values, and normal CSF protein levels [10, 12, 14, 20, 25].

Prognosis, however, appears to have improved in the 1990s, possibly because of better recognition of the disease and earlier implementation of intensive supportive care [14].

"Mild forms" of ANE with unilateral reversible thalamic involvement are recently described. In these rare, "milder" cases of ANE, some authors observed that cerebellar and pontine abnormalities disappeared during the course of illness [24]. These patients show a good prognosis and the pathological process, despite the term "necrotizing", is partially or totally reversible [12, 25]. The reasons for the different grades of pathologic and clinical involvement remain unknown.

Management

There is no specific therapy for ANE but, in some patients, the clinical status improved with the administration of corticosteroid at the acute stage [1, 2, 19]. Their clinical usefulness, however, has not yet been determined systematically. Hypothermia and early anticytokine therapy was suggested to be therapeutic in some cases of ANE [17].

We present another patient who exhibited a "severe" clinical and neuroradiological picture promptly treated with intravenous methylprednisolone and immunoglobulin therapy. This case showed a precocious remarkable neurological improvement, "mild" clinical sequelae and an almost complete regression of multiple bilateral brain lesions assessed by CT scan and MRI.

Illustrative case

In February 2003, a 3-year-old girl was admitted to a local hospital because of a generalized tonic–clonic convulsion lasting around 45 min. Two days before admission, she presented with fever, rhinorrhea, sore throat, and othalgia treated with antibiotic therapy. At arrival to the emergency service, she was still affected by uncontrolled seizure and her body temperature was 37.8°C. She was treated with 0.05 mg/kg of intravenous lorazepam with clinical resolution of the status epilepticus but with no improvement on the level of consciousness that rapidly deteriorated in the next 12 h. A CT scan was performed which showed hypodense lesions in both thalami (Fig. 1). After a few hours, she had a second seizure that required intubation to protect the airway, and close respiratory and cardiovascular

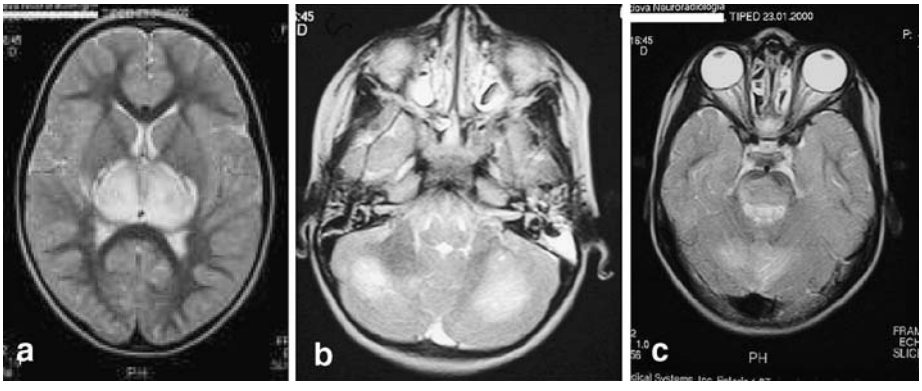

Fig. 2 Axial T_2-weighted (MRI) images show symmetric thalamic hyperintensities bilaterally (**a**), associated with lesions on the deep cerebellar white matter (**b**), and pontine tegmenta (**c**)

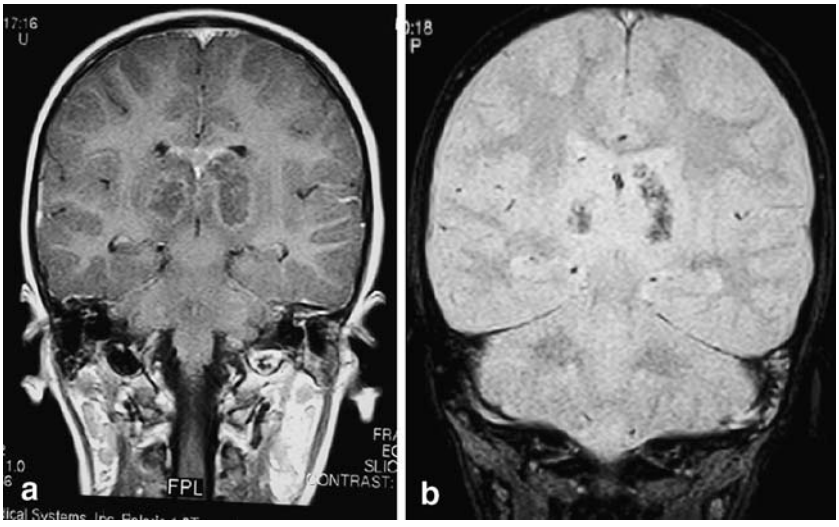

Fig. 3 Coronal contrast-enhanced T_1-weighted (MRI) images show bilateral ring-like enhancement around central hypointense thalamic lesions (**a**), which appear hemorrhagic on T_2-weighted gradient-echo image (**b**)

monitoring. Thus, she was admitted to the pediatric intensive care unit of our Department of Pediatrics, University of Padua.

At admission she was sedated and paralysed with otherwise normal physical examination results. Body temperature was 38°C. An electroencephalogram showed generalized slow wave activity. All biochemical and hematological values were normal, including full blood count, serum urea, electrolytes, glucose, creatine kinase, glutamic–oxaloacetic transaminase, glutamic–pyruvic transaminase, ammonia, amino acids and plasma lactate, prothrombin time, and partial thromboplastin time. Urinalysis and urine organic acids were normal. Blood cultures did not show any bacterial, viral, or fungal growth. Anti-DNA antibodies and antinuclear antibodies were negative as well as serum viral antibody titers, including influenza A and B, herpes simplex, human herpes virus 6 (HHV-6), Epstein–Barr, adenovirus, echovirus, parvovirus, coxsackievirus A and B, varicella-zoster and rubella, on the second and sixth day.

The cerebrospinal fluid showed high pressure (25 cmH_2O), no significant increase in cells (one mononuclear and three red cells) and lactate (2.2 mmol/l, normal values 1.1–2.2) and mildly elevated glucose (4.3 mmol/l, normal values 2.2–3.9) and proteins (0.9 g/l, normal values 0.15–0.45). CSF cultures showed no bacterial growth and no evidence of viral infection by polymerase chain reaction including herpes simplex 1 and 2. Antibodies against *M. pneumoniae* were not detectable and immunoelectrofocusing for oligoclonal banding showed a normal pattern. CSF, repeated at day 6, showed normalization of the biochemical parameters.

Brain MRI, performed at the admission to the Pediatric Intensive Unit, showed multifocal symmetrical lesions in brainstem, cerebellum, and thalami (Fig. 2). Contrast-enhanced T_1-weighted images showed a bilateral ring-like pattern of thalami (Fig. 3a), which appear hemorrhagic on T_2-weighted gradient-echo image (Fig. 3b). Diffusion-weighted MR images in this acute stage revealed bilateral symmetric hyperintense lesions in the thalami with ring-like hyperintensity (Fig. 4). Cerebral angio-MRI was normal.

The patient was treated with phenytoin, intravenous immunoglobulin (1g/kg/day for 2 days) and methylprednisolone (20 mg/kg e.v. for 3 days), followed by prednisone (50 mg/day per os for 7 days).

Her consciousness progressively improved, but MRI findings obtained on the seventh day of hospitalization persisted to be altered (Fig. 5).

After 22 days of hospitalization, she was discharged with mild ataxia and spasticity (major on the left side), dysarthria, and left strabismus.

She was followed up 1.5 months later, when she showed a marked improvement of dysarthria, spasticity, and ataxia, with persistence of left abducens nerve deficiency. Bilateral

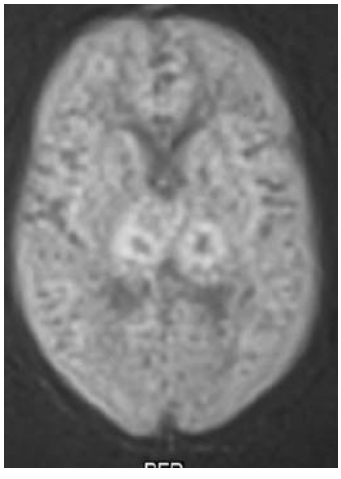

Fig. 4 Diffusion-weighted MRI: bilateral symmetric hyperintense lesions with ring-like features in the thalami

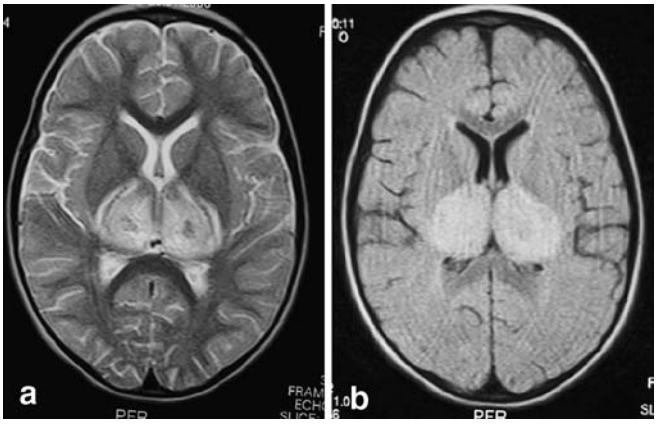

Fig. 5 At 5-day follow-up, axial T_2-weighted (MRI) image shows mild reduction of hyperintensities in thalami with central hypointensity (**a**). Fluid-attenuated inversion-recovery image confirms the bithalamic hyperintensities (**b**)

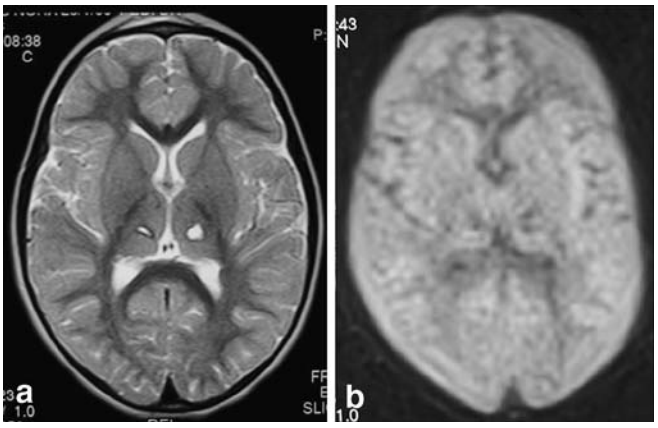

Fig. 6 At 5-month follow-up, MR examination shows thalamic lacunar lesions in T_2 (**a**) and T_1 images without contrast enhancement (not shown), without the ring-like features on diffusion-weighted image (**b**)

tremor and myoclonus of action of both arms were evident. Brain MRI showed a remarkable reduction of all cerebral lesions, with persistence of a small foci in the central portion of thalami (Fig. 6).

After another 3 months, the clinical conditions were further improved with the persistence of dysarthria, left strabismus, and myoclonus. MRI findings were unchanged.

The clinical and neuroradiological findings were stable after 24 months.

This case showed severe clinical manifestations with extensive bilateral cerebral involvement in the first cerebral MRI. We suppose that early therapy based on combined steroid and intravenous immunoglobulin might have interfered with the acute process, leading to a mild clinical and neuroradiological outcome.

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