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Evaluation of non-infectious causes of acute encephalopathy in the pediatric patients

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Abstract

Aim: The aim of the study is to evaluate and classify the less common non-infectious causes of acute encephalopathy (AE).

Materials and Methods: The clinical, etiological, radiological and electrophysiological findings of the patients who were diagnosed with AE were analyzed retrospectively. The patients were classified using the flow chart of the new evidence-based guidelines for AE.

Results: Noninfectious causes were identified in 22 of 45 (%48) patients diagnosed with AE[%49.8 were male]. Mean age of patients was found 3.4±4.6 (0-17.5) years. Seven (%31.8) patients had status epilepticus and prolonged seizures, five patient (%22.7) had asphyxia and stroke, four patient (%18.1) had metabolic encephalopathy, two (%0.9) had AE due to cytokine storm, two (%0.9) had autoimmunity-related AE, and two had intoxication as the cause.

Conclusion: Acute encephalopathy (AE) is a neurologic emergency condition with high morbidity and mortality. The etiology of AE covers a broad spectrum. Since treatment depends on the underlying etiology, time is of essence for diagnosis. Following an established algorithm greatly facilitates diagnosis and treatment.

Introduction

Acute encephalopathy (AE) is defined as an acute or subacute global, functional alteration of mental status [1]. Encephalopathy can present a very broad spectrum of symptoms ranging from mild to severe, such as partial memory loss or subtle personality changes, lethargy, coma, or death [2]. Incidence ranges between literature, but is generally between 3,2 and 7.5 per 100,000 patient-years. Risk of mortality is 5.6% [3]. Generally, AE is a reversible condition when the causative factor is successfully eliminated, and patients can return to the baseline status. Accordingly, it is vital to identify the causative factors [4]. Etiologically, the most common causes of acute encephalitis are central nervous system infections [5]. The aim of the study is to evaluate and classify the less common non-infectious causes of acute encephalopathy (AE).

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Materials and Methods

This was a single-center retrospective study. Ethical approval was obtained from the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with the number of 2021/514/215/17, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Informed parental consent was not obtained due to the retrospective design of the study. Patient data was used without the inclusion of any identifying information.

Definitions

Acute encephalopathy (AE) is defined as having an acute onset of consciousness impairment, personality change, or a Glasgow Coma Scale score < 11 and the continuation of this clinical picture until an appropriate treatment is administered. It is distinguished from other diseases, such as encephalitis, and other causes of altered mental status like adverse effects of drugs, and psychogenic seizures [6]. Patients aged 0–18 who applied to the emergency, pediatric

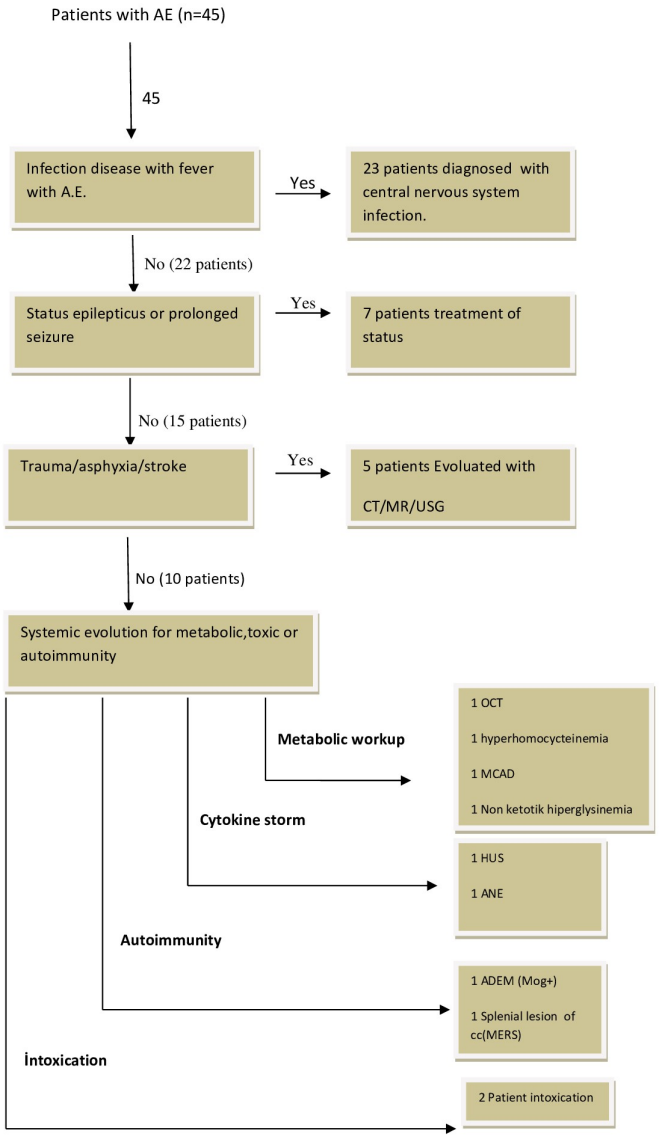

Figure 1. Flow chart of the diagnosis and treatment of acute encephalopathy (AE).

intensive care, and pediatric neurology departments between the years 2019 and 2021 were included in the study. Age, cranial magnetic resonance imaging (MRI) and electroencephalography (EEG) findings, clinical findings , underlying diseases , and prognosis of the patients included in the study were recorded in an excel file. The patients were classified using the flow chart of the new evidence-based guidelines for AE reported by Mizuguchi et al. (2020) [7].

Results

Among the 45 patients who met the criteria for AE, 23 patients with central nervous system infection were excluded from the study and causes of AE other than central nervous system infection were included in the study. Noninfectious causes were identified in 22 of 45 (%48) patients diagnosed with AE[%49.8 were male]. Mean age of patients was found 3.4±4.6 (0-17.5) years. Seven (%31.8) patients had status epilepticus and prolonged seizures, five patient (%22.7) had asphyxia and stroke, four patient (%18.1) had metabolic encephalopathy, two (%0.9) had AE due to cytokine storm, two (%0.9) had autoimmunity-related AE, and two had intoxication as the cause. Demographic data of the patients, symptoms at admission, duration of AE, and cranial MRI and EEG findings are presented in Table 1. The flow chart used for diagnosis and treatment is presented in Figure 1.

Discussion

Encephalopathy is defined as dysfunction affecting the level of consciousness. There are many systemic conditions that cause AE, and some are reversible. Therefore, it is important to determine the starting points in AE evaluation [6]. In this present study, the most common noninfectious cause of AE was status epilepticus, prolonged seizure, and temporal lobe epilepsy (30.4%). Status epilepticus is one of the most common neurologic emergency that needs immediate treatment to decrease morbidity and mortality. If not treated in a timely manner, it carries the risk of serious complications such as brain edema and death [8]. Among the patients included in this study, only two patients developed brain edema as a complication of status epilepticus. One of these patients was diagnosed with nonketotic hyperglycinemia. In a previous study, Sarah et al. (2018) reported that mortality rates were higher in patients with status epilepticus compared to patients with brain edema on cranial MRI. [9]. Similarly, in this study, patients with a pathological condition detected on cranial MRI had a longer recovery period from AE and a higher frequency of neurological deficits. Nonconvulsive status epilepticus (NCSE) is a clinical disorder defined as prolonged seizure activity without major motor signs. Therefore NCSE accompanies AE. Generalized epilepsies such as absence epilepsy, as well as focal epilepsies, also cause NCSE [10]. In our study, focal status epilepticus was detected on the temporal regions via EEG in two patients of the epilepsy group who presented with acute personality change, and the patients returned to baseline after intravenous phenytoin administration. As Pascual reported in 2007, some focal epilepsies, especially temporal lobe epilepsy, may present with automatism and acute changes in consciousness, and EEG is an important tool to distinguish this [11]. In this study, trauma, asphyxia, and stroke were identified as the second most common noninfectious cause of AE following status epilepticus. Trauma history could not be obtained in the first anamnesis of our 2 patients who were found to have trauma as the cause of AE. So trauma should also be investigated in patients in whom no trauma history was obtained in the anamnesis, since it is a common cause of AE. USG in small infants and CT in older patients is an important diagnostic tool for the detection of hemorrhage. However, diffusion MRI is recommended for the diagnosis of stroke and diffuse axonal damage [12].

Furthermore, four (14.2%) patients had metabolic causes of AE—ornithine transcarbamylase deficiency, fatty acid oxidation defect, nonketotic hyperglycinemia, and homocysteinemia, respectively. Of these patients, one patient died, and two patients showed severe neurological deficits. These patients were identified as one of the groups with the highest mortality and morbidity risks. Inherited metabolic

Table 1. Clinical findings of the patients.

Patient ID	Age (year)	Symptom	Etiology	Duration of AE	Prognosis	Brain MRI (Magnetic Resonance Imaging)	EEG findings	Underlying cause
Pt1	0	Coma	Brain edema	400 h	Discharced with ND	Diffusion restriction in both cerebral hemispheres, cortical sulci, corpus callosum and bilateral thalamus.	NA	Fatty acid oxidation defect
Pt2	0	Irritability	Intracranial hemorrage	36 h	Ex	Late subacute subgleal hematoma	NA	Normal
Pt3	0	Stupor	Stroke	84 h	Discharced with ND	Diffusion restriction in white matter in the right lateral ventricle and in the periventricular white matter in the left lateral ventricle.	NA	NA
Pt4	1	Coma	Brain Edema	88 h	Discharced with ND	Diffuse cerebral edema.	Diffuse delta slowing	Non-ketotic hyperglycin-emia
Pt5	1	Coma	Asphyxia	36 h	Ex	Restricted diffusion in the cerebellar hemispheres, basal ganglia and cerebral cortex in particular, the perirolandic and occipital cortices.	NA	SMA
Pt6	0	Lethargy, irritability	Intracranial hemorrhage	576 h	Come back to baseline	Intraventricular hemorrhage	NA	Normal
Pt7	3	Coma	Acute necrotizing encephalitis	430 h	Discharced with ND	T2W/FLAIR hyperintensity in cerebral cortex, cerebellar and biocipital white matter. mixed signal intensity symmetrical with hemorrhage in the thalamus.	NA	Normal
Pt8	8	Altered mental status	Status	48 h	Come back to baseline	Normal	NA	Normal
Pt9	1	Coma	Status	72 h	Come back to baseline	Diffuse brain edema	NA	Epilepsy
Pt10	5	Altered mental status	Status	24 h	Come back to baseline	Normal	NA	Epilepsy
Pt11	5	Altered mental status	Status	168 h	Come back to baseline	Normal	NA	Wolf hichhorn sendromu
Pt12	3	Altered mental status	Status	24 h	Come back to baseline	Dandy walker malformation. No diffusion restriction.	1.5hz slow wave discharge in temp region	Epilepsy
Pt13	3.5	Altered mental status	Status	120 h	Come back to baseline	Hydocephalus+vp shunt/ No diffusion restriction.	NA	Hydocephalus+ vp shunt
Pt14	4.5	Alterd mental status personality change	Transient splenial lesion.	120 h	Come back to baseline	Diffusion restrictions in the splenium part of the corpus callosum and the medial anterior part of the right cerebellar hemisphere.	Diffuse delta slowing	Normal
Pt15	3	Deep coma	HUS	720 h	Discharced with ND	Diffusion restriction in the bilateral basal ganlia.	Diffuse delta slowing	Normal
Pt16	3	Alterd mental status personality change	OCT deficiency	144 h	Ex	Partial corpus callosum agenesis. Colpocephali in the posterior horns of the lateral ventricle/ diffuse brain edema is present.	NA	Normal
Pt17	6.5	Alterd mental status personality change	ADEM	144 h	Come back to baseline	Contrasting patchy demyelinating lesions were observed in the white matter and thalamus.	Diffuse delta slowing	Normal
Pt18	15.5	Alterd mental status personality change	Drug intoxication	36 h	Come back to baseline	Normal	Normal	Normal
Pt19	17.5	Alterd mental status personality change	Drug intoxication	24 h	Come back to baseline	Normal	Normal	Normal
Pt20	13	Alterd mental status personality change	Trauma	720 h	Come back to baseline	Diffusion restriction areas in the splenium of the corpus callosum and the left parieto-occipital region.	Normal	Normal
Pt21	17	Alterd mental status personality change	Focal status	16 h	Come back to baseline	Normal	Periodic 1 hz slow delta waves on the left temporal region	Epilepsy mental retardation
Pt22	1	Alterd mental status	Hyperhom-osisteinemia	620 h	Discharced with ND	Normal	Slowing of the bacground activity with multifocal discharges	Hyperhom-osisteinemia

ND: neurological deficit, NA: not available, h: hour, sma: spinal muscular atrophy HUS: hemolytic uremic syndrome, OCT deficiency: ornithine transcarbamylase deficiency ADEM: acute demyelinating encephalomyelitis.

diseases with acute presentation can be subgrouped into five categories, intoxication type, disorders with reduced fasting tolerance, impaired energy metabolism, neurotransmitter disorders, and disorders in which no specific emergency treatment is needed. The first four of these five groups cause acute and subacute encephalopathies. The laboratory parameters performed in a possible metabolic emergency should include all parameters that are important for making urgent therapeutic decisions. Glucose, blood gases, ketones in urine, serum ammonia level, lactate, blood count, CRP, electrolytes, ALT, AST, CK, creatinine, urea, uric acid, coagulation studies should be performed as the first line investigation of the metabolic emergencies. Further investigations may have to be performed depending on the clinical presentation and basic investigation results; these may include serum or plasma levels of insulin, carnitine in plasma and/or urine, tandem mass spectrometry, plasma amino acids, homocysteine, urine organic acids, urinary orotic acid, or reducing substances in urine. If needed, amino acid and glucose levels in the cerebrospinal fluid should also be checked depending on the condition [13-15].

Acute encephalopathy (AE) associated with cytokine storm (hypercytokinemia) usually display systemic inflammatory response syndrome (SIRS). SIRS is a systemic reaction that results in the overproduction of inflammatory cytokines in response to infections, trauma and other factors. Anti-inflammatory therapy is the most important treatment approach for this type of AE [16]. In this study, two patients had SIRS. Patient 1 exhibited hemolytic uremic syndrome (HUS) with cranial involvement 2 weeks after salmonella infection, and Patient 2 developed acute necrotizing encephalopathy (ANE) after influenza. Both these patients had neurological deficit during discharge. This was one of the groups with the highest mortality. Cranial MRI findings and systemic inflammatory response markers were effective in the diagnosis of both patients. ANE is a specific type of AE. Its occurrence is usually preceded by a viral febrile illness followed by rapid disruption [17]. The most common viral agent is the influenza virus. Although there is no consensus on the treatment protocol, it has been revealed that early corticosteroid and anti-inflammatory therapies are effective on prognosis. [18]. Cases of HUS exhibiting AE and brain involvement are very rare and have a poor prognosis. Eculizumab is the recommended treatment modality [19]. In this study, one patient with HUS also received eculizumab treatment and was discharged with neurological deficit. The last neurological examination of the patient revealed that acute encephalopathy was completely resolved, but the patient developed dystonic movement disorder due to the involvement of the basal ganglia. This patient is still under follow-up in the neurology outpatient clinic.

Reversible splenial lesion of the corpus callosum (MERS) is a clinicoradiological syndrome that can be concerned to infectious and noninfectious situations. The most common symptoms are altered mental status, speech abnormalities, personality changes, seizures, muscle weakness, and headache [20]. Various conditions such as infection, discontinuation of antiepileptic drugs, altitude sickness, Kawasaki disease, electrolyte-related abnormalities like hyponatremia or hypoglycemia have been reported as the etiology of MERS [21]. The pathophysiology of the lesion reflects cytotoxic edema and reversible demyelination. In this study, reversible splenial lesion of the corpus callosum was detected in one patient; etiological cause could not be determined. The patient's condition improved after 1 week, and the patient returned to baseline status. Cases wherein patients recover within 24 hours to 21 days have been reported in the literature. Moreover, the prognosis of many patients with MERS is good regardless of treatment. Methylprednisolone pulse and high-dose gamma globulin therapies are not always indicated [22]. Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system that includes multifocal areas of the white or gray matter, such as the thalamus and rarely the spinal cord; it mainly affects pediatric patients and mostly occurs 10-15 days after infection or vaccination. Current guidelines recommend checking anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in case of ADEM [23]. In this study, the patient diagnosed with ADEM was positive for anti-MOG antibody. In this patient, encephalopathy resolved on the 5th day of pulse steroid treatment. In the 10-month follow-up, the patient was negative for anti-MOG antibody and did not have a new attack.

Two patients (0.08%) whose etiology could not be detected via metabolic screening, EEG, and cranial MRI findings had a history of intoxication. This was the patient group in which it took the longest to identify the etiology. Diagnosis was achieved via either toxicology or urinalysis findings or the patients' personal statements after having been treated of encephalopathy. Therefore, it is very important not to neglect intoxications as the etiology of AE.

Limitation of our study is that it is a single center study and although very rare causes of AE were reported, the number of patients is relatively small.

Conclusion

AE is a condition of neurologic emergency with high morbidity and mortality, and its etiology covers a broad spectrum. Its treatment depends on the underlying etiology; therefore, timely diagnosis is essential. In addition, diagnosis and treatment can be facilitated by following an established algorithm.

Conflict of interest

The authors declare no competing interests.

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Ethics approval

This study was approved by the local ethics committee of Kartal Dr. Lutfi Kirdar City Hospital with the number of 2021/514/215/17.

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