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Ifosfamide related encephalopathy: The need for a timely EEG evaluation

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ABSTRACT

Background: Ifosfamide is an alkylating agent useful in the treatment of a wide range of cancers including sarcomas, lymphoma, gynecologic and testicular cancers. Encephalopathy has been reported in 10–40% of patients receiving high-dose IV ifosfamide.
Objective: To highlight the role of electroencephalogram (EEG) in the early detection and management of ifosfamide related encephalopathy.
Methods: Retrospective chart review including clinical data and EEG recordings was done on five patients, admitted to MD Anderson Cancer Center between years 2009 and 2012, who developed ifosfamide related acute encephalopathy.
Results: All five patients experienced symptoms of encephalopathy soon after (within 12 h–2 days) receiving ifosfamide. Two patients developed generalized convulsions while one patient developed continuous non-convulsive status epilepticus (NCSE) that required ICU admission and intubation. Initial EEG showed epileptiform discharges in three patients; run of triphasic waves in one patient and moderate degree diffuse generalized slowing. Mixed pattern with the presence of both sharps and triphasic waves were also noted. Repeat EEGs within 24_h of symptom onset showed marked improvement that was correlated with clinical improvement.
Conclusions: Severity of ifosfamide related encephalopathy correlates with EEG changes. We suggest a timely EEG evaluation for patients receiving ifosfamide who develop features of encephalopathy.
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1. Introduction

The alkylant ifosfamide has proven efficacy in the treatment of a wide range of cancers including sarcomas, lymphoma, gynecologic and testicular cancers [1]. Ifosfamide and its metabolites can cross the blood brain barrier and cause central nervous system (CNS) toxicities. CNS toxicity is mostly characterized by metabolic encephalopathy of varying severity; confusion, lethargy, agitation, somnolence, and seizure [2]. Ifosfamide related encephalopathy is reported in 10–40% patients receiving the drug, thus being responsible for a high rate of treatment-related morbidity [3,4]. Although ifosfamide related encephalopathy is generally reversible after withdrawal of the drug, rapidly progressive encephalopathy leading to death has been reported [4]. Moreover, there have been increasing reports of non-convulsive status epilepticus in patients receiving ifosfamide [1,2]. It is estimated that up to 65% of patients receiving ifosfamide have abnormal EEG finding [5]; however, data showing a correlation between EEG abnormalities and severity of ifosfamide encephalopathy is lacking. Here we report, using a case series design, a correlation between EEG abnormalities and severity of ifosfamide related encephalopathy in five patients receiving high dose ifosfamide.

2. Methods

Retrospective chart review including clinical data and EEG recordings was done on five patients, admitted to MD Anderson Cancer Center between years 2009 and 2012, who developed ifosfamide related acute encephalopathy.

3. Results

There were 2 women and 3 men patients aged 24 to 33 years. At the time of admission one patient was receiving levetiracetam for seizure disorder related to metastatic brain disease (case 5). All of our patients received combination chemotherapy including high dose IV ifosfamide (dose range: 1.5–3 g/m^2) for different tumors. All five patients experienced symptoms of encephalopathy soon after (within 12 h–2 days) receiving ifosfamide; two patients developed generalized convulsion and confusion, one patient experienced confusion and disorientation, one patient becomes delirious and restless, and one patient was in coma due to NCSE that required intensive care unit admission and intubation. On neurologic examination, none of our cohort displayed focal neurologic deficits or abnormal involuntary movements. A summary of these cases is provided in Table 1. In our

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Table 1
Summary of five cases of ifosfamide related encephalopathy.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (yrs)/Gender	31/Male	24/Female	30/Female	26/Male	34/Male
Underlying tumor type	Transitional bladder cancer	Ewing's sarcoma	Large B cell lymphoma	Synovial sarcoma	Testicular cancer
IFOS dose	1.5 g/m2 for 3 days	1.5 g/m2 for 2 days	1.5 g/m2 for 1 day	2 g/m2 for 7 days	2 g/m2 for 4 days
Concomitant chemotherapy	Cisplatin; Paclitexel	Etoposide	Rituximab; Etoposide	Doxorubicin	Etoposide; Carboplatin
Cycle number	2	7	3	5	2
Clinical presentations	GTC lasting 4 min; confusion	Confusion; disorientation; automatism	Non-responsive; coma	GTC seizure lasting 1 min, confusion	delirium, confusion + blurring of vision
Time of onset	12 h	24 h	24 h	24 h	36 h
Intervention	IV hydration, IV MB, IFOS ceased	IV hydration, IV MB, IFOS ceased	IV hydration, IV MB, IFOS ceased	IV hydration, IV MB, IFOS ceased	IV hydration, IV MB, IFOS ceased
AED used	Phenytoin, diazepam	No AED	Levetiracetam, Midazolam, Diazepam	Levetiracetam	Levetiracetam
Duration of encephalopathy	resolved within 24 h	resolved within 24 h	resolved within 1 wk	resolved within 12 h	resolved within 24 h

AED: Anti-epileptic drug; GTC = generalized tonic-clonic seizure; IFOS = ifosfamide; IV = intravenous; MB = methylene blue.

Table 2
Pertinent laboratory values.

	Case 1	Case 2	Case 3	Case 4	Case 5
Na + (136–147 mEq/L)	137	136	140	142	144
Alb (3.2–4.8 g/dL)	3.9	3.6	4	3.7	2.6
ALT (7–56 units/L)	<12	<12	19	35	45
AST (15–43 units/L)	15	26	24	27	43
T.Bil (0.1–1.2 mg/dL)	<0.1	1.3	0.4	0.3	0.6
NH4+ (11–35 μmol/L)	<11	<11	<11	<11	17
Creatinine clearance	40	123	100	101	60
Initial EEG findings	Isolated epileptiform discharges	Moderate diffuse slowing; triphasic waves	Non-convulsive status epilepticus	Intermittent epileptiform discharge	Moderate diffuse gen brain slowing; triphasic waves
Repeat EEG findings	Improved background, gen slow	Subtle slowing with reactive background	Epileptiform discharges abated; sedation	Improved background; epileptiform discharges abated	Improved background, mild gen slowing

Alb = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Na + = sodium; NH4+ = ammonium; T.Bil = total bilirubin. Note repeat EEG recordings were obtained within 24 h of symptom onset.

cohort blood and urine cultures, serum TSH, Vitamin B1 and B12 levels, and paraneoplastic panel were normal. Moreover, serum chemistry profiles were normal except in one patient who had hypoalbuminemia and in two patients who had baseline mild chronic kidney disease (see Table 2). Post contrast brain MRI was unremarkable except in one case, with history of brain metastasis status post surgical intervention, which revealed post-surgical changes (case 5). CSF examination was unremarkable except in one case that tested positive for the presence of malignant cells (case 2). Standard bedside prolonged EEGs (41–60 min) at the onset of encephalopathy showed epileptiform discharges in three patients with background moderate slowing; run of classic metabolic triphasic waves in one patient and moderate degree diffuse generalized slowing in all patients. Mixed pattern with the presence of both sharps and triphasic waves is also noted. A summary of laboratory values including description of initial and repeat EEG findings is provided in Table 2. Examples of EEG in the described patients are provided in Fig. 1A–C.

Patients with EEG showing epileptiform discharges were treated with anti-epileptic medication. The two patients with generalized convulsion were treated with lorazepam 2 mg IV followed by standard IV doses of levetiracetam or phenytoin. The patient with NCSE received 2 mg IV lorazepam followed by midazolam infusion at a rate 40 mg/h in addition to a scheduled dose of levetiracetam. The patient with prior history of seizure disorder was continued on his home dose of levetiracetam (case 5). Repeat EEGs within 24 h of symptom onset i.e. after ifosfamide cessation and/or initiation of AED revealed marked improvements; isolated epileptiform discharges converted to generalized slowing (cases 1, 3, and 4), spike and sharp waves were abolished, and triphasic waves (case 2) and severe diffuse slowing were replaced by mild to moderate degrees of slow waves (in all 5 cases; see Table 2). These EEG improvements correlated to the clinical improvements: seizures were controlled, alteration in mental status improved, and the patient with NCSE started to follow commands. None of our cohorts, except the patient with prior history of seizure disorder, required long term AED as symptoms of encephalopathy abated within 1–4 days after last ifosfamide administration.

4. Discussion

Ifosfamide-induced encephalopathy is mostly seen with high drug doses, shorter infusion times, and previous or concomitant central nervous system diseases [6]. Other risk factors include; low serum albumin, previous or concomitant use of cisplatin, pre-existing hepatic and/or renal impairments, and history of prior ifosfamide related encephalopathy [4,7]. All of our patients received combination chemotherapy including high dose IV ifosfamide (dose range: 1.5–3 g/m2) for different tumors. One patient had a concomitant treatment with cisplatin. Our cohort had history of previous high dose ifosfamide administrations (see Table 1) with no prior record of ifosfamide related encephalopathy. All of these patients had normal

Fig. 1. Panel of representative EEG recordings at onset of encephalopathy in the five cases who developed ifosfamide related encephalopathy. Panel A: EEG recordings in case 4 showing frequent diffuse and rhythmic delta slowing and triphasic waves. Panel B: EEG recordings in case 3 showing generalized medium- to high-amplitude activity of spike and wave, and sharp- and slow-wave complexes consistent with NCSE. Panel C: EEG recording in case 5 showing generalized diffuse slowing, with sharp waves and spikes. Note, EEG recording parameters: amplitude, 1 cm = 70 μV, interval between two thick vertical lines = 1 s.