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Clinical and Electroencephalographic Characteristics of Ifosfamide-Related Encephalopathy

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Abstract

Purpose—Ifosfamide can lead to a syndrome of central nervous system (CNS) toxicity. Here we investigate the clinical and electroencephalographic (EEG) characteristics of patients with ifosfamide-related encephalopathy.

Methods—Retrospective data were collected on patients from Memorial Sloan Kettering Cancer Center, who developed encephalopathy associated with ifosfamide between 2007 and 2017. Patients who had an EEG performed were included. Clinical and laboratory data were retrospectively collected. Each EEG recording was reviewed and compared with the originally documented EEG report.

Results—Sixteen (16) patients with ifosfamide-related encephalopathy were included, with primary tumors consisting of lymphoma (N=9), sarcoma (N=4), poorly differentiated ovarian cancer (N=1), neuroblastoma (N=1), and papillary serous adenocarcinoma (N=1). Laboratory results ruled out other etiologies of encephalopathy. Generalized periodic discharges (GPDs) with or without triphasic morphology were seen most commonly (N=9), with a distinct pattern of interspersed intermittent background attenuation seen in 5 patients. Background slowing and intermittent rhythmic delta activity (N=4), bursts of bilateral synchronized delta activity (N=2), and frontal predominant intermittent delta activity (N=1) were also seen. One patient demonstrated a pattern consistent with nonconvulsive status epilepticus. While most patients experienced resolution of symptoms, those who died demonstrated a variety of EEG abnormalities. Abnormal movements were common, with six patients demonstrating characteristic orofacial myoclonus.

Conclusions—Ifosfamide related encephalopathy commonly results in a distinct pattern of GPDs admixed with intermittent background attenuation on EEG. Abnormal movements, in particular orofacial myoclonus, are also common. Recognizing these clinical and EEG features might lead to early detection of ifosfamide-related encephalopathy.

Keywords

Ifosfamide; encephalopathy; electroencephalography; generalized periodic discharge

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INTRODUCTION

Ifosfamide, an alkylating chemotherapeutic agent, is used alone or in combination with other agents to treat various solid tumors such as ovarian, testicular, head and neck, and sarcomas as well as lymphoma (2,10). In addition to complications such as myelosuppression, hemorrhagic cystitis, nausea, and vomiting, a syndrome of ifosfamide-related central nervous system (CNS) toxicity has been described (14). Treatment with high-dose ifosfamide can result in an encephalopathy which commonly occurs from 12 hours to 6 days after treatment initiation (10,14). The CNS symptoms are along a spectrum of severity. The CNS symptoms typically improve within 48–72 hours after discontinuation (10,14), however encephalopathy can in some cases lead to coma and death (17). Predisposing factors for ifosfamide-related encephalopathy include higher doses, poor functional status at treatment initiation, concomitant cisplatin treatment, renal failure, hepatic insufficiency, and low serum albumin levels (2,14).

The toxic metabolite chloroacetaldehyde may cause encephalopathy due to the depletion of cerebral glutathione (10,18). Ifosfamide's parent compound, cyclophosphamide, does not undergo dechloroethylation, which liberates chloroacetaldehyde, and likely accounts for its lack of CNS toxicity (14). The metabolite chloroethylamine may also contribute by inhibiting flavoprotein dependent mitochondrial respiration, resulting in accumulation of reduced nicotinamide adenine dinucleotide (NADH), preventing the dehydrogenation of chloroacetaldehyde and promoting its accumulation (17). To date there is no effective treatment for the reversal of ifosfamide toxicity however methylene blue and thiamine have been used with varying efficacy (10,21).

Ifosfamide-related encephalopathy often prompts evaluation with electroencephalography (EEG). Several patterns of EEG changes in ifosfamide-related encephalopathy have been described, however all have been limited to small case reports. Nonconvulsive status epilepticus (NCSE) can occur in ifosfamide-related encephalopathy, although it seems to occur in a minority of affected patients (5,9). It has been suggested that EEG changes may correlate with the severity of ifosfamide-related toxicity with generalized slowing or generalized period discharged (GPDs) with triphasic morphology in minimally affected patients, epileptiform discharges in those moderately affected, and NCSE in the most severely affected (5).

In this study, we sought to evaluate the EEG changes in a cohort of patients with ifosfamide-related encephalopathy in association with their clinical presentations in order to uncover clinical and electroencephalographic features unique to ifosfamide-related encephalopathy.

METHODS

Patient data was retrospectively analyzed from a single tertiary care center, Memorial Sloan Kettering Cancer Center (MSKCC). Search results included all patients who developed ifosfamide-related encephalopathy during hospitalization and yielded 41 patients. Between the years of 2007 and 2017, 16 of those patients had long-term video EEG records available for review. Clinical and laboratory data were retrospectively abstracted for each patient

through the electronic medical record. Each EEG was reviewed and interpreted by a board-certified neurophysiologist (XC). Continuous video EEG recordings were performed with Natus 32-channel computerized EEG system with standard 10–20 electrode montages. Standard American Clinical Neurophysiology Society (ACNS) terminology (7) was used for interpretation. Study subjects had full blood cell counts, comprehensive chemistry panels, ammonia, thyroid stimulating hormone (TSH), and vitamin B12 levels to exclude common causes of encephalopathy. The MSKCC institutional review board approved this study.

RESULTS

We included 16 patients with ifosfamide-related encephalopathy and continuous EEG monitoring. Demographic data and clinical information are shown in Table 1. Age range was from 14 to 70 years, with a median of 55 years. There were 11 female and 5 male patients. Malignancies being treated included lymphoma (N=9), sarcoma (N=4), poorly differentiated ovarian tumor (N=1), neuroblastoma (N=1), and papillary serous adenocarcinoma (N=1). Time from ifosfamide infusion to symptoms ranged from 1–2 hours to 60 hours (median 24 hours). Patients had been treated with 1500 mg/m² to 5000 mg/m² ifosfamide (median 2500 mg/m²). Treatments included methylene blue (N=13), thiamine (N=10), urine alkalinization (N=1), and decreased infusion rate (N=1). The majority experienced resolution of their symptoms (N=11). Symptoms did not resolve and eventually led to death in 5 patients.

The presentation of each patient included disorientation, delirium, or inattentiveness (N=16), and the majority had somnolence or lethargy (N=13). Aphasia or mutism was present in 4 patients, while only one presented with a generalized tonic clonic seizure, and one with hallucinations. Two patients had an unsteady gait on presentation (Table 2). The most common EEG feature was GPDs with triphasic morphology (Figure 1A, N=9) followed by a special pattern of GPDs interspersed with periods of background attenuation (2–4 seconds) between discharges, which was seen in 5 patients (Figure 1B,C). Background slowing (N=4) and intermittent rhythmic delta activity were also seen (N=4). Less common was occasional frontally predominant generalized rhythmic delta activity (GRDA, N=1) or bursts of bilateral synchronized rhythmic delta activity (N=2). EEG was consistent with NCSE in only one patient. Of those who died during the hospitalization, EEG was characterized by NCSE and bursts of bilateral synchronized rhythmic delta activity (N=2), diffuse background slowing (N=1), or GPDs with triphasic morphology with interspersed background attenuation (N=2). Myoclonus was observed in 4 patients, characterized by multifocal myoclonus (N=3), or arm myoclonus (N=1). Six patients also exhibited what we hereafter will refer to as orofacial myoclonus including grimacing, grunting, eye opening and closing, smacking and chewing movements. We did not observe any choreiform or dystonic movements. None of them demonstrated epileptiform activities such as eyelid fluttering, gaze deviation or unilateral facial muscle twitching. These patients demonstrated characteristic facial movements, which we were also able to capture and revealed no clear EEG correlation except muscle artifacts. The movements did not seem to be EEG state dependent.

The pattern of GPDs with triphasic morphology admixed with attenuation was further investigated with amplitude-integrated EEG. As shown in Figure 2, over a period of 1 minute of recording, 12 episodes of attenuation were recorded (indicated with arrows),

lasting up to four seconds. The periods of attenuation were characterized by voltages as low as 5 μ V (Figure 2). Further examination of the GPDs with triphasic morphology revealed a maximum positive amplitude from 16 to 42 μ V. There was a slight anterior to posterior lag (Figure 1B, blue arrow). This pattern did not persist during sleep (Figure 1D).

Neuroimaging was obtained in 13 of the patients, with no intracranial abnormalities detected in 11 patients. Magnetic resonance imaging (MRI) performed on patient number 8 demonstrated small foci of restricted diffusion in the posterior left frontal lobe and right occipital lobe consistent with acute infarct. MRI brain performed on patient number 13 revealed minimal periventricular and subcortical chronic white matter microvascular ischemic changes.

Routine laboratory studies were obtained for each patient. Albumin was commonly low (median 3.10, interquartile range (IQR) 2.58–3.18). Significant renal impairment was not present (median creatinine 1.1, IQR 0.7–1.4; median estimate glomerular filtration rate 60, IQR 47–60). Other causes of encephalopathy were not found with no patients demonstrating elevated ammonia, low vitamin B12, or abnormal TSH. Most had normal liver function (median ALT 19.0, IQR 11.5–46.5; median AST 25.0, IQR 13.8–41.5).

DISCUSSION

Ifosfamide treatment is known to result in serious encephalopathy with high mortality rates as confirmed in our study; however, no unique clinical or EEG features have hitherto been reported. Herein, we report clinical and EEG features of ifosfamide-related encephalopathy in the largest cohort of patients to date. We show that ifosfamide-related encephalopathy, in addition to causing background slowing, rhythmic delta activity and GPDs with or without triphasic morphology, commonly produces interspersed periods of background attenuation lasting 2 to 4 admixed with GPDs with triphasic morphology. We also report a characteristic pattern of orofacial myoclonus during the period of encephalopathy.

Time to onset of symptoms (median 24 hours), fits with a previously reported range of 12 to 146 hours (11,14), however in patient number 11 symptoms occurred after only 1–2 hours (Table 1). This may be attributed to early detection of mild symptoms in this patient, with resolution of symptoms occurring after decreasing ifosfamide. Our results are consistent with higher doses of ifosfamide correlating with symptom severity. Median ifosfamide dose among those who died was 5000mg/m². No other etiologies for encephalopathy were found. Significant renal impairment was not present and only mild transaminitis was found, with no patients demonstrating an elevated ammonia. However, our data support the previously reported association between low serum albumin and ifosfamide-related encephalopathy (2) with our patients having a median albumin of 3.1.

White matter has been implicated in the development of GPDs with triphasic morphology (8). Reverberating corticothalamic inputs may suppress the sequential activation of midline thalamic reticular nuclei, which are thought to play a role in the development of GPDs with triphasic morphology. Acquired white matter disease impairs corticothalamic input, allowing for the thalamic generation of GPDs with triphasic morphology (8,16). However, in the

patients reported herein, neuroimaging revealed only mild white matter disease in one patient. Additional work will be needed to understand the mechanisms underlying the electrophysiological patterns seen in patients with ifosfamide toxicity. However, it is possible that, similar to ammonia, ifosfamide may affect cerebral gamma-aminobutyric acid tone and postsynaptic neuron inhibition (8,16).

Orofacial myoclonus has not been reported to our knowledge in associated with ifosfamide toxicity. One previous case report notes, as non-convulsive status epilepticus, eyelid fluttering and facial myoclonus correlating with 0.5 to 1 second periods of attenuation following GPDs with triphasic morphology (19). Here we observed stereotypical involuntary facial movements, which we have referred to as orofacial myoclonus in 6 patients and attenuation following GPDs with triphasic morphology in 5 patients (31%). Orofacial movements are commonly observed as a side effect of chronic use of dopamine D2 receptor antagonists, such as typical antipsychotic drugs or metoclopramide. The underlying mechanism is thought to be due to a compensative over-activity of dopaminergic neuronal activity or reduced GABAergic neuronal activity (1). These orofacial myoclonus resemble the movement disorders observed in other acute, diffuse brain dysfunction such as anti-NMDA receptor encephalitis, where epileptic and non-epileptic events are intermixed (3,6). Using the Naranjo adverse drug reaction probability assessment tool, ifosfamide is considered the probable culprit in our series with a score of 7 (13). Our findings suggest that orofacial myoclonus occur commonly and may be characteristic of severe ifosfamide-related encephalopathy, even in the absence of correlated epileptic discharges.

These movements have not been described in prior case reports or series. The series by Savica *et al* describes movement disorders as associated with ifosfamide neuro-toxicity and notes the presence of generalized myoclonus as being a sign of CNS toxicity. By contrast in our series, generalized myoclonus was observed only observed in 4 patients, with more orofacial myoclonus present in 6 patients (15). Our series also founds that orofacial myoclonus can occur independently of generalized myoclonus. Moreover, in comparison to Wernicke's which can lead to a syndrome of encephalopathy with a movement disorder, most commonly choreoathetosis and dystonia (12,20), the myoclonus observed in our case series is distinct. The movements observed are intermittent, recurrent, spasmodic and would occur with no associated eyelid fluttering, ophthalmoparesis or gaze deviation. Further, there was no EEG correlate to suggest that these movements are epileptic in nature.

It has been suggested that a continuum of EEG findings exists, with slowing representing mild and NCSE representing severe ifosfamide-related encephalopathy (5). Among the patients who died in our study, only one had NCSE, while others had GPDs with triphasic morphology with attenuation or slowing. Therefore, our results do not support the notion that the most severe cases of ifosfamide-related encephalopathy are associated with NCSE. GPDs with triphasic morphology admixed with periodic attenuation and background slowing may also be associated with poor outcomes.

Our results demonstrate that EEG pattern of GPDs with interspersed background attenuations associated with characteristic orofacial myoclonus are associated with ifosfamide-related encephalopathy. While GPDs with triphasic morphology have been

reported in a variety of metabolic encephalopathies (4), the periods or marked attenuation seen on conventional EEG montages and highlighted on amplitude-integrated EEG seem to be related to ifosfamide-related encephalopathy and may be associated with poor outcome. These patterns may help to identify patients whose encephalopathy is due to ifosfamide treatment and may provide insight into outcomes. We suggest that prolonged video EEG recording should be performed in patients with encephalopathy thought to be due to ifosfamide treatment to facilitate the detection of these EEG patterns and orofacial myoclonus.

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Figure 1:

Representative electroencephalogram (EEG) patterns. Conventional bipolar EEG montage is shown for a patient with a pattern of generalized period discharges (GPDs) with triphasic morphology (A) with each triphasic wave indicated by a blue arrow. A characteristic example of GPDs with triphasic morphology waves (gray arrows) followed by periods of attenuation of 2–3 seconds noted with gray lines (B). Example of an EEG (C) demonstrating longer periods of attenuation (4 seconds, red line). EEG during sleep demonstrating a poorly organized background without GPD (D).

Figure 2.
Amplitude-integrated EEG demonstrating 12 episodes of brief attenuation of background amplitude within a period of one minute. Each black arrow indicates one period of attenuation.

Table 1:

Demographics and clinical data

#	Age	Gender	Primary Cancer	Dose mg/m ²	Time to Symptom Onset (h)	EEG Features	Abnormal Movements	Initial Symptoms	Outcome
1	53	F	Sarcoma	2500	24	Triphasic, Frontal predominant intermittent delta	Yawning	Hallucinations	Resolved
2	17	M	Lymphoma	5000	48	R frontal seizure, NCSE, bursts of bilateral synchronized delta	None	Disoriented, inattentive	Deceased
3	45	F	Lymphoma	2500	24	Intermittent delta activity	None	Disoriented, inattentive	Deceased
4	51	M	Lymphoma	1500	36	Diffuse mild background slowing	Orofacial myoclonus	Disoriented, inattentive	Improved
5	64	F	Lymphoma	5000	24	Triphasic waves with various attenuation	Arm myoclonus, orofacial myoclonus	Disoriented, inattentive	Improved
6	68	F	Lymphoma	2500	24	Triphasic, attenuation	None	WFD, inattentive	Resolved
7	70	F	Lymphoma	2500	24	Background slowing	None	Disoriented	Resolved
8	58	M	Lymphoma	5000	36	Slowing, intermittent delta	Tremulous, multifocal myoclonus	Inattentive, paucity of speech	Resolved
9	46	F	Sarcoma	2500	24	Triphasic, attenuation	Tremor, orofacial myoclonus, yawning	Lethargy, GTC seizure	Resolved
10	69	M	Lymphoma	5000	24	Triphasic, attenuation	Myoclonic jerking, orofacial myoclonus	Inattentive	Deceased
11	20	F	Sarcoma	2800	1	Normal	None	Disoriented, inattentive	Resolved
12	57	F	Lymphoma	5000	48	Delta, triphasic, attenuation	None	Unsteady gait, disoriented	Resolved
13	57	F	Sarcoma	2500	24	Triphasic	Orofacial myoclonus	WFD, unsteady gait	Resolved
14	31	F	Poorly Differentiated Ovarian Tumor	1500	48	Slowing, triphasic	Orofacial myoclonus	Lethargy, Inattention	Resolved
15	14	M	Neuroblastoma	1500	60	Bilateral synchronized delta	None	Lethargy	Resolved
16	66	F	Papillary Serous Adenocarcinoma	2000	24	Triphasic, intermittent delta	Myoclonic jerks	Aphasia	Resolved

Table 2:

Presentation of Patients with Ifosfamide toxicity

Clinical Presentation	N=	EEG Characteristics	N=
<i>Disorientation/Delirium/Inattentive</i>	16	<i>Generalized periodic discharges with triphasic morphology</i>	9
<i>Aphasia/Dysphasia</i>	8	<i>Frontal predominant generalized rhythmic delta activity</i>	1
<i>Somnolence/Lethargy</i>	13	<i>NCSE</i>	1
<i>Seizures</i>	2	<i>Bursts of bilateral synchronized delta</i>	2
<i>Diffuse Tremor/Myoclonus</i>	5	<i>Intermittent delta activity</i>	4
<i>Facial Myoclonus</i>	9	<i>Background slowing</i>	4
<i>Hallucinations</i>	1	<i>Attenuation</i>	5
<i>Unsteady Gait</i>	2		