A novel case of prolonged Ifosfamide encephalopathy and long-term treatment with methylene blue: a case report and review of literature

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Abstract

Background: Encephalopathy following Ifosfamide treatment is a well-described phenomenon that is typically treated with Methylene Blue (MB). Chloroacetaldehyde, a potentially neurotoxic metabolite of Ifosfamide is hypothesized to cause this encephalopathy. Current guidelines for treatment is to stop Ifosfamide and provide supportive care. MB acts to inhibit Chloroacetaldehyde formation and has been described as a therapy and prophylaxis for Ifosfamide-encephalopathy. MB is effective within 30 min and lasts up to 3 days. Prolonged encephalopathy and MB therapy has not been described in the literature as lasting longer than 30 days following treatment.

Case presentation: We present the case of an 11-year-old female with autistic spectrum disorder and recurrent episodes of severe somnolence for 7 months following Ifosfamide therapy for her Non-Germinomatous Germ Cell Tumor (GCT). Periods of somnolence occurred prior to receiving cranial RT. Administration of MB gave immediate but limited response, with resolution of somnolence lasting 1-2 days between administrations. The somnolence could not be explained by neuroimaging or laboratory evaluation, but EEG indicated persistent encephalopathy.

Conclusion: A literature review determines that neurotoxicity is a side effect of Ifosfamide, but this effect has not been described persisting longer than 30 days. Our case continued to require treatment with MB for 7 months following cessation of therapy. We report these novel clinical findings, and hypothesize that there could be a genetic/metabolic component linking this reaction to Ifosfamide with the case patient’s pre-existing autism. This possible association may also correlate to the already-established link between autism and the development of GCTs. This hypothesis leads to further discussion on the suitable usage of Ifosfamide in children with co-morbidities and the necessity of screening prior to its usage.

Keywords: Somnolence, Ifosfamide, Methylene blue, Encephalopathy

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Background

Germ Cell Tumors (GCT) account for 3% pediatric brain tumors and are subcategorized into Germinomas (G) and Non-Germinomatous (NG) GCT [1]. Most NGGCT involve the pineal or pituitary glands [2]. Pineal tumors often present with symptoms of hydrocephalus including lethargy, vomiting and mental status changes and...
pituitary tumors often present with polyuria or growth
disruption.

Ifosfamide is a chemotherapeutic agent, which is a syn-
thetic analog of cyclophosphamide. Side effects of Ifosfa-
mide can include hair loss, bladder irritation and central
nervous system (CNS) toxicity [3, 4]. These CNS tox-
icities include encephalopathy, lethargy and personality
changes. During the metabolism of Ifosfamide, Chloroac-
etaldehyde is produced which is a potentially neurotoxic
metabolite that crosses the blood-brain barrier and has
been suggested as the etiology behind Ifosfamide enceph-
aloopathy [5].

The incidence of CNS toxicity following Ifosfamide
therapy is estimated between 10 to 20 % [2]. High doses
(>2G/M2/Day) of Ifosfamide correlate to higher rates of
adverse effects, however, encephalopathy can be dem-
onstrated at any dose and specific blood levels of Ifosfa-
mide have not been clearly linked to the development of
neurotoxicity. CNS toxicity usually presents acutely fol-
lowing drug administration and subsequently resolves
following drug discontinuation [5]. Certain studies have
demonstrated the effects lasting for up to 30 days fol-
lowing treatment [6]. Current guidelines for Ifosfamide
encephalopathy include treatment cessation, supportive
care and the use of Methylene Blue (MB) as a therapeutic
and prophylactic treatment. Risk factors for Ifosfamide-
encephalopathy include hypoalbuminemia and previous
CNS disease [7].

MB is a therapy for Ifosfamide-encephalopathy and
research suggests MB's mechanism involves inhibition of
monoamine oxidase which is involved in Chloroacetale-
dehyde formation. Potential adverse effects of MB include
discoloration of the skin, vomiting and hemolytic ane-
mia [8]. MB is effective within 30 min and can last up to
3 days.

**Case presentation**

We present the case of an 11 yr female with a back-
ground of autism spectrum disorder of moderate sever-
ity (which presented in early childhood) who presented
with 4 months of cognitive changes. Brain MRI detected
a pineal tumor with hydrocephalus and spinal metasta-
sis. GCT markers beta-HCG and alpha-fetoprotein (AFP)
were elevated within the Cerebrospinal fluid (CSF). They
underwent right frontal VP (ventriculoperitoneal) shunt
insertion and tumor pathology reported an NGGCT. She
was initiated onto the high-risk treatment arm: COG
ACNSO122, which includes 6 cycles of induction chemo-
therapy (alternating cycles of Carboplatin/Etoposide and
Ifosfamide/Etoposide and craniospinal radiation with
boost to the tumor bed. Each cycle of Ifosfamide included
1800 mg/m²/day for 5 days. The patient's baseline physical
exam was unremarkable.

During the 4th course of chemotherapy (Ifosfamide/
Etoposide) the patient developed sequelae of Ifosfa-
mide encephalopathy which included drowsiness, con-
fusion and somnolence. As per protocol for Ifosfamide
toxicity (grade 2/3), treatment was started with MB (IV,
1 mg/kg, BID). Within hours of initiation, patient ori-
entation returned to baseline. Multidisciplinary discus-
sion was held to discuss the risks/benefit of continued
Ifosfamide treatment and a decision was made to con-
tinue treatment with close observation and continued
use of MB. During the 6th cycle (Ifosfamide/Etoposide,
without concurrent use of the anti-emetic Aprepitant),
4 months after treatment initiation, MB was prophylac-
tically used from Day — 1. On day 4 of this cycle, how-
ever, the patient developed somnolence. CT and MRI
brain were normal, EEG demonstrated mild encepha-
lopathy. Due to concerns of early hydrocephalus, VP
shunt revision was performed, however, the somno-
ulence persisted only resolving following MB treatment.

Ifosfamide metabolites, ammonia levels, thiamine lev-
els, lumbar puncture and blood gas were all unchanged
from their baseline. AFP/HCG, following initial eleva-
tion at diagnosis, then normalized and remained so
on serial analysis, EEG continued to demonstrate mild
encephalopathy both prior to, and following MB. Lev-
etiracetam was trialed with no benefit noted.

During the radiation course, 7 months following
diagnosis, the patient required multiple readmissions/ 
reviews for recurrent episodes of somnolence. Shunt
revision did not alter these episodes. CT and MRI did
not note new pathology and serum AFP and B-HCG
values continued to be within normal limits. EEG con-
tinued to demonstrate encephalopathy. During all these
episodes, MB was used and within 30 min of initia-
tion, the patient was at baseline. Physical exam demon-
strated generalized reduced awakening with no other
focal neurological findings.

After discussion, radiation therapy was initiated
under close observation and no clinical deterioration
was reported. Following this course of treatment, the
patient was fully alert and orientated. They underwent
further neurocognitive testing and they continue to
have episodes of recurrent somnolence, however, there
were significant cognitive deficits affecting behavior
and memory. MRI of brain and spine showed no evi-
dence of disease and blood/CSF markers remained
negative. An “Invitae” genetic predisposition work-up
was completed (including oncologic panel for germ-
cell tumor predisposition and metabolic panels which
included assessments for inborn errors of metabolism),
which thus far does not note any significant findings.
The patient continues to be in remission without evi-
dence of disease.
Discussion and conclusion
Ifosfamide-related encephalopathy is a phenomenon well described in the literature. The first reported case of Ifosfamide encephalopathy and MB treatment was documented in 1996 [9] and describes IE as occurring between 48h and 30 days following treatment [10]. Prolonged Ifosfamide encephalopathy and prolonged treatment are novel findings that have not been described in the pediatric population [5]. A case series does describe two reports of prolonged Ifosfamide encephalopathy in an adult population, including a 41 year old woman who developed cognitive dysfunction following Ifosfamide infusion [11]. She was not treated with MB and her neurologic abnormalities persisted beyond 10 years. Encephalopathy can occur at any doses of Ifosfamide, however higher doses do predispose to a higher incidence of adverse effects.

Due to our case patient’s diagnosis of autism, we reviewed the literature for any correlation between the diagnosis of autism and the presence or severity of Ifosfamide encephalopathy. Whilst no specific data is published describing this correlation, there is established data associating Autism Spectrum Disorder (ASD) with the development of GCTs [12]. Therefore, we hypothesize that a diagnosis of ASD may also predispose to the toxic effects of Ifosfamide. Similarly, whilst no single physiological pathway is validated for this link, we propose that several plausible theories exist, for example the established effect of Chloroacetaldehyde on Glutathione, imbalance of which is a suggested a pathway to ASD [13, 14]. This hypothesis may indicate a need for more extensive preliminary screening of comorbid candidates requiring Ifosfamide. We acknowledge that this hypothesis is currently only supported by sparse observational reports, but we hope that this case will prompt others to report similar findings.

We also consider that neurocognitive disorders (such as autism spectrum disorder), may be confounders when analyzing the presentation of ‘somnolence’. We note, for example, that autism is a risk factor for sleep disturbance [15] and this can lead to neuropsychiatric complications. Our case patient and caregiver did not report significant sleep disturbance and overnight EEG was not indicative of sleep pathology. Polysomnography may help to qualify these episodes of ‘somnolence’.

The neuroprotective effects of MB was evaluated in a case review of 52 patients, which concluded that MB is an effective treatment for Ifosfamide encephalopathy [16]. The study also demonstrated that prophylactic treatment with MB leads to fewer and milder cases of Ifosfamide encephalopathy [17]. The mechanism of Ifosfamide encephalopathy centers around a metabolite, Chloroacetaldehyde, which is hypothesized to be inhibited via treatment with MB. Chloroacetaldehyde is typically eliminated within a 24-h period [18]. To investigate if delayed elimination of Chloroacetaldehyde is causing the observed symptoms, a metabolome would need to be performed on the patient. If metabolic signatures of Chloroacetaldehyde are identified following cessation of Ifosfamide, this would support the hypothesis that prolonged Ifosfamide encephalopathy is caused by increased retention of Chloroacetaldehyde. Blood levels of Ifosfamide in our patient were noted to be normal, however specific levels have not been validated when linked to encephalopathy.

In conclusion, Ifosfamide-induced encephalopathy is a well-described toxicity which usually lasts for a period of days to weeks following treatment. MB is described as a therapy for this encephalopathy, but prolonged encephalopathy and treatment with MB after several months of cessation of treatment with Ifosfamide has not been previously reported. We highlight this case in order contribute to the ongoing research on the usage of Ifosfamide in children with co-morbidities and the potential value of genetic or metabolic screening prior to its use.

Abbreviations
MB: Methylene Blue; GCT: Germ Cell Tumor; G: Germinomatous; NG: Non-Germinomatous; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; VP: Venticuloperitoneal; ASD: Autism Spectrum Disorder; EEG: Electroencephalogram.

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Authors’ contributions
GC & MK drafted and formatted this report. AS, LP, KK, NZ and KK were part of the patient’s treatment team and were involved in editing this report. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Not Applicable.

Consent for publication
Written informed consent was obtained from the patient’s parent for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Competing interests
The authors declare that they have no competing interests.
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