Reversible Encepahlopathy Induced by Ifosfamide with Brain Imaging

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Daoud Ali Mohamed, MD[1], Arthur Semedo, MD[1], Boris Adeyemi, MD[1], Leila Hessissen, MD[2], Maria El Kababri, PhD[2], Nazik Allali, PhD[1], Latifa Chat, PhD[1], and Siham El Haddad, MD[1]

Abstract

Chemotherapy may be responsible for central and/or peripheral neurotoxicity. These neurological complications are frequent but little known. Some molecules are more providers, responsible for acute or late complications, sometimes not reversible. Some manifestations such as acute encephalopathy and acute reversible encephalopathy are increasingly understood. We report here a case of acute ifosfamide-induced encephalopathy (EII) with brain damage resolved after discontinuation of this treatment in a 13-years-old child.

Keywords

reversible encephalopathy induced by ifosfamide, chemotherapy, brain damage, MRI

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Introduction

Cancer treatment especially involving chemotherapy, may later be responsible for central and/peripheral neurotoxicity.[1,2] These neurological complications are frequent but little known. Not anodyne, sometimes they can be irreversible. Some molecules are more providers, responsible for acute or late complications.[2] Methothrexate and ifosfamide are the molecules that often cause acute encephalopathy. Other molecules, such as 5-FU, IL-2, cyclophosphamide can be responsible for encephalopathies but less frequently. Ifosfamide is widely used in solid malignant tumors.[2] Encephalopathy is one of the serious side effects of ifosfamide. Knowledge and detection of neurological complications of ifosfamide are essential in the management of ifosfamide encephalopathy.[3,4]

Case Report

This is a 13-year-old boy with no pathological history, hospitalized in the hematology-oncology department for abdominal rhabdomyosarcoma. The history of the disease goes back to 3 months of his hospitalization by the installation of abdominal pains with progressive deterioration of the general condition. On admission, the patient was conscious with a GCS score 15/15, apyretic with impaired general condition, weight = 30 kg. Physical examination revealed a large papable abdominal mass extending from the epigastric to the right hypochondrium. Ultrasound then abdomino-pelvic Computed tomography (CT) scan confirmed the diagnosis by objectifying a median retro-peritoneum mass. The biological assessment was normal. An ultrasound-guided biopsy was performed. The histological diagnosis was in favor of an undifferentiated sarcoma. Extension workup revealed lung micronodules and peritoneal nodules under the liver. The child was put on anti-cancer treatment combining ifosfamide-vincristine-actinomycin (IVA) and Mesna^{R} to prevent urological toxicity. The dosages of these molecules were: Ifosfamide (3 g/m^2/day) 3 g/day as an infusion administered over 3 hours, vincristine (1.5 mg/m^2/day) 1.5 mg by slow direct intravenous injection, actinomycine (1.5 mg/m^2/day) 1.5 mg as a slow direct intravenous injection and Mesna^{R} at a

[1]Pediatric Radiology Department , Children's Hospital of Rabat, University Hospital of Ibn Sina Rabat, Rabat, Morocco
[2]Hematology-Oncology Department, Children's Hospital of Rabat, University Hospital of Ibn Sina Rabat, Rabat, Morocco

Corresponding Author:
Daoud Ali Mohamed, Department of Radiology, Rabat Children's Hospital, Mohammed V University, Agdal, Rabat, Morocco.
Email: daoudkabir88@gmail.com

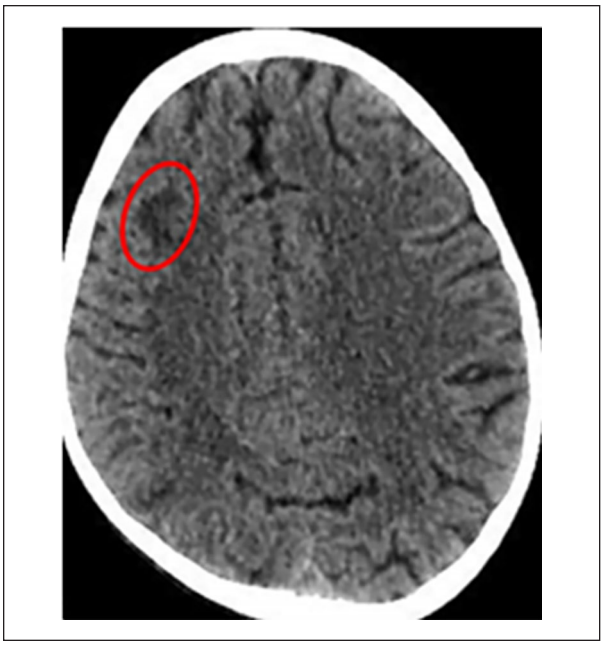

Figure 1. Spontaneous brain CT scan with enhanced contrast, axial slice, showing hypodense lesions under the right frontal cortices of subacute aspect.

dose of 900 mg/day. Ten days after treatment, the child developed seizures. An emergency computed tomography was performed showing hypo-dense right frontal brain lesions (Figure 1). There was no sensory or motor deficit. To better characterize, we performed a cerebral magnetic resonance imaging (MRI) which objectified the subcortical lesions in T2 and FLAIR hyper signal, in T1 hypo signal, without restriction of the diffusion sequence and without enhancement after injection of gadolinium (Figure 2). Knowing the side effect of ifosfamide, the IVA-based protocol was stopped and modified by the Vincristine-Actinomycin-Cyclophosphamide (VAC) protocol. The evolution was marked by the definitive cessation of seizures without other signs. No biological abnormality was detected and no specific treatment was added outside of the new protocol. Two weeks after stopping ifosfamide, we performed a control brain MRI which revealed that the previously described brain lesions had disappeared (Figure 3). Faced with the favorable clinical course and the disappearance of the brain lesions, the diagnosis of IIE was retained.

Discussion

Methotrexate and ifosfamide are the 2 chemotherapy agents most responsible for neurological complications in the treatment of chemotherapy.[2] Ifosfamide is an oxazaphosphorus alkylating agent derived from nitrogen mustard with anti-tumor activity. It is a structural analogue of cyclophosphamide known as endoxan often used in germ cell tumors, lymphomas, and sarcomas. The main toxicities of ifosfamide are urological and neurological toxicity. Urological toxicity manifests as hemorrhagic cystitis but can be avoided by concomitant administration of a uroprotector such as urometoxan or Mesna^{R}.[3,5,6] The neurological toxicity of ifosfamide can range from drowsiness, confusion, hallucinations, seizures, and coma, sometimes leading to death in more severe cases in children. The National Cancer Institute has classified IIE into 4 grades: grade 1—mild somnolence or agitation, grade 2—moderate symptoms, Grade 3—severe symptoms, mild hallucinations, or a stuporous conditions, Grade 4—State of hallucinations, seizures, or coma.[4,7,8] These neurological complications are not rare but less known and are generally reversible after stopping treatment.[4,7] They are seen in 10% to 40% of pediatric and adult patient and the time to onset usually varies from a few hours to 72 hours after using ifosfamide, sometimes up to a week.[4,9] In our case, the seizures were observed within 10 days of treatment. This delay in diagnosis is probably due to the fact that the neurological complications of ifosfamide are not well known. Secondly, because our child was in poor general condition, early neurological signs such as drowsiness, confusion, and hallucinations may not have been taken into account. It is believed that many factors are involved in the occurrence of ifosfamide-induced encephalopathy, such as WHO score >2, hypoalbuminemia, high creatinine level or renal failure, tumor with osteosarcoma or rhabdomyosarcoma type histology, concomitant use of aprepitant, duration of administration <6 hours.[4,5,10,11] The method of injection and the dose of administration have been described but not significant in children. Pharmacologically, it has been reported that the EII is very high with the Ifosfamide EG^{R} form than with the Haloxan^{R} form 21.1% versus 4.3%.[4,10,12] In our case, the child had an altered general condition but not assessed according to the WHO score, the duration of administration of ifosfamide (HaloxanR form) was 3 hours well below the duration recommended in the literature which is 6 hours. We did not notice any abnormality in the biological evaluation.[5,10] All these risk factors are discussed because there are few multivariate studies.[4] The occurrence of IIE is unpredictable, but caution is advised when using this antimitotic in patients with these risk factors. Reintroduction of ifosfamide is possible but should be done with a slower infusion. Some authors recommend using methylene blue, sometimes thiamine, before using ifosfamide, but their effectiveness has not been proven.[4] The diagnosis

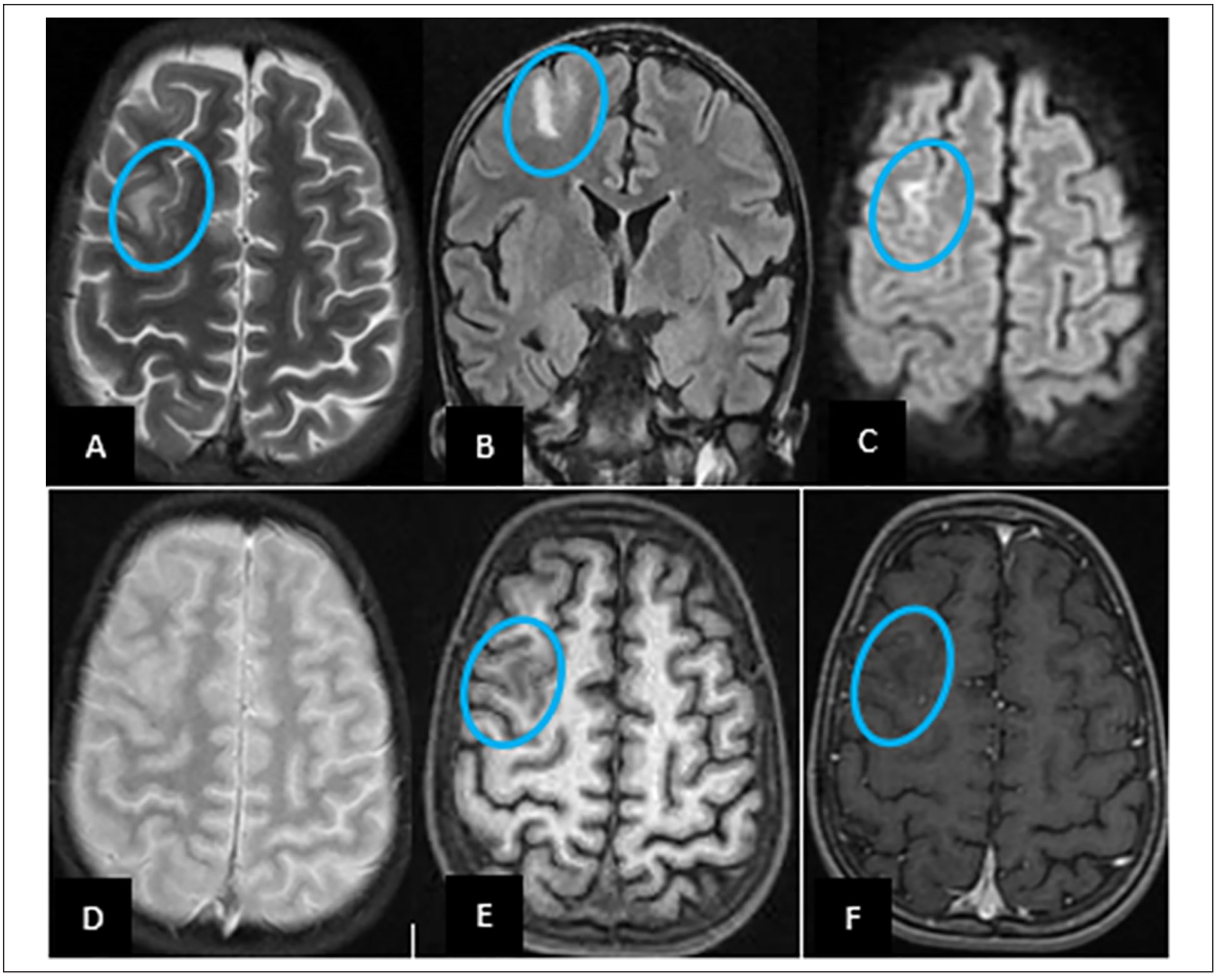

Figure 2. Initial MRI. (A, B, C) T2 sequence axial section, flair sequence in coronal section and diffusion sequence in axial section showing hyper signal lesions under right frontal cortices. (D) T2 * sequence not showing a hypo signal. (E and F) Sequence T1 not injected and T1 after injection of gadolinium in axial slices, showing lesions in hypo signal T1 not injected and without contrast uptake after injection.

of IIE is clinical. The biological assessment can be requested for hypoalbuminemia, renal function. According to various studies, the EEG shows commonly generalized periodic discharges with or without triphasic morphology suggesting toxic-type encephalopathy.[12] CT or MRI brain imaging is most often normal, suggesting toxic-type encephalopathy associated with ifosfamide.[4,7] In our case, in our case, brain lesions were observed on CT and MRI which disappeared 2 weeks after stopping ifosfamide. In our case, faced with the favorable clinical course and the disappearance of the brain lesions, the diagnosis of IIE was retained. Almost all of the literature studies on ifosfamide-induced encephalopathy have not reported brain damage seen on brain imaging.

Conclusion

Ifosfamide is an alkylating agent responsible for acute or late neurological complications. One of the serious side effects of ifosfamide is encephalopathy. It is believed that many factors are involved in the occurrence of ifosfamide-induced encephalopathy. Knowledge and detection of neurological complications of ifosfamide are essential in the management of ifosfamide encephalopathy. Brain imaging is often normal. In our case, we observed cerebral lesions which disappeared after stopping treatment. Could this be due to early diagnosis by early brain imaging? Or by not performing brain imaging, especially in the pediatric population?

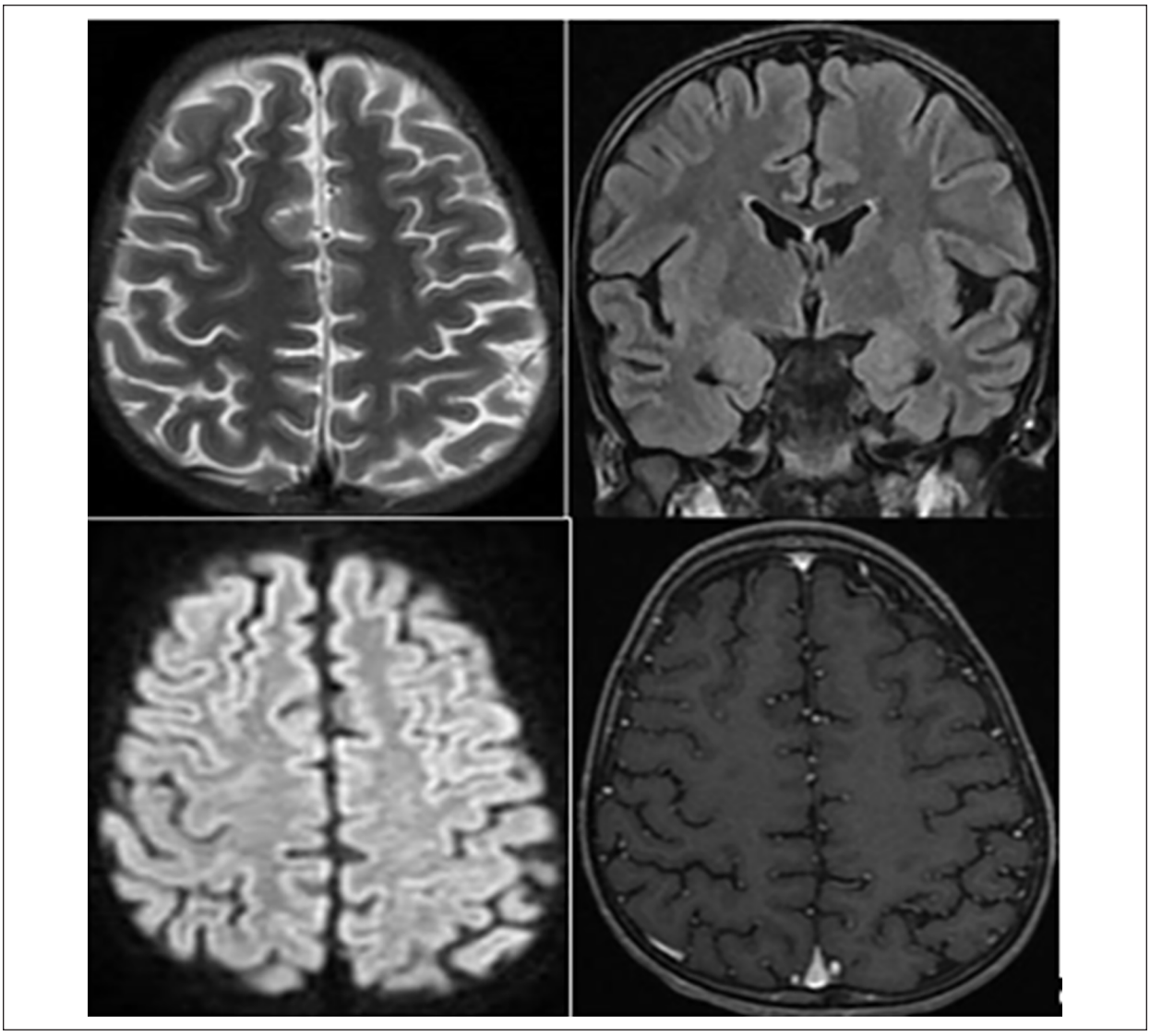

Figure 3. MRI control: disappearance of the lesions described on the initial MRI in all the sequences.

Author Contributions

All authors contributed equally in this work.

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Patient Consent Statement

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ORCID iD

Daoud Ali Mohamed https://orcid.org/0000-0002-7426-4821

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