Clinical commentary

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Drug-resistant epilepsy after treatment for childhood acute lymphocytic leukaemia: from focal epilepsy to Lennox-Gastaut syndrome

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ABSTRACT – Drug-resistant epilepsy, not associated with acute brain complications or central nervous system leukaemic involvement, can develop in patients treated for acute lymphocytic leukaemia during childhood. It has been postulated that this rare complication may be due to CNS oncological treatment neurotoxicity, related to intrathecal drugs, such as methotrexate, and brain radiotherapy. We report four patients who developed drug-resistant epilepsy sometime after receiving treatment for acute lymphocytic leukaemia. All patients were female and received intrathecal methotrexate. One received additional intrathecal cytarabine, and two concomitant brain radiotherapy. Two developed Lennox-Gastaut type syndrome, one multifocal epilepsy, and one focal epilepsy related to a radiotherapy-induced cavernous angioma. The development of drug-resistant epilepsy after treatment for acute lymphocytic leukaemia is a rare complication that may vary, from focal epilepsy to an epileptic encephalopathy. This may appear even years after the treatment has finished and is most likely associated with treatment-related neurotoxicity.

Key words: drug-resistant epilepsy, acute lymphocytic leukaemia, Lennox-Gastaut syndrome, methotrexate

Acute lymphocytic leukaemia (ALL) is the most frequent form of cancer in children (Howlader *et al*., 2016). Successful treatment for children with ALL involves administration of a multidrug regimen and includes therapy directed to the central nervous system (CNS). Seizures are a rare complication of ALL, appearing in around 13% of patients (Maytal *et al*., 1995). The most common presentation is acute symptomatic seizures occurring during the induction and consolidation phases of therapy. However, a proportion of these patients will later develop epilepsy which is not associated with acute brain complications or CNS leukaemic involvement (Ochs *et al*., 1984).

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It has been postulated that this may be due to neurotoxicity related to the CNS oncological treatment, such as intrathecal methotrexate (MTX) and brain radiotherapy. Focal and generalized epileptic syndromes have been reported, even years after the ALL treatment has finished in patients in remission. What is remarkable is that this rare complication may behave as drug-resistant epilepsy (Fasano and Bergen, 2009).

Here, we report four patients who developed medically intractable epilepsy sometime after receiving treatment for ALL, and review the drug-resistant epileptic syndromes described in the survivors of childhood ALL.

Case studies

Patients of the senior author, referred to the outpatient Seizure Clinic of the Montreal Neurological Hospital and Institute between 1998 and 2015, were reviewed. Based on chart reviewing, we identified four patients treated for childhood ALL, who presented with drug-resistant epilepsy. We defined drug-resistant epilepsy as failure of adequate trials of two tolerated, appropriately chosen and used, antiepileptic drugs (AEDs) to achieve sustained seizure freedom. None of the patients had leukaemic involvement of the CNS or acute neurological complications. They had no other significant medical or neurological antecedents, and presented no known family history of neurological disorders. We reviewed the ALL treatment received, age at epilepsy onset, seizure types, EEG recordings, epileptic syndromes, antiepileptic treatment, and outcome. The patients' demographic and clinical data are summarized in *table 1*.

Case 1

A 29-year-old female who had ALL at 1.5 years of age. Induction and maintenance chemotherapy included prednisone, MTX, cyclophosphamide, vincristine, and L-asparaginase. CNS prophylaxis consisted of intrathecal MTX and whole-brain radiotherapy (18 Gy). She first showed a cognitive decline with seizures starting at approximately age 5, two years after the end of her oncological treatment. She developed Lennox-Gastaut syndrome (LGS) with significant intellectual disability, atypical absences, myoclonic seizures, head-drop, and drop attacks. Her EEGs showed generalized slow spike-and-wave complexes and an abnormal background activity. Brain MRI was unremarkable. Brain CT revealed bilateral frontal cortical and subcortical calcifications. (*figure 1A, B*). She received multiple AED regimens and ketogenic diet. She had an anterior callosotomy at 10 years old, and finally had a vagal nerve stimulator (VNS) at the age of 20. Currently, she has daily seizures.

Case 2

A 23-year-old female who had ALL at 2.5 years of age. Induction and maintenance chemotherapy included MTX and 6-mercaptopurine. CNS prophylaxis consisted of intrathecal MTX and cytarabine. She started with seizures during the maintenance therapy at 3.5 years old, and this treatment was stopped. She developed moderate intellectual disability with atypical absences, head drop, drop-attacks, and generalized seizures, a picture consistent, at least in part, with LGS. Her EEGs showed generalized slow spike-and-wave complexes, polyspike-and-wave complexes, and an abnormal background activity. Imaging revealed bilateral calcifications in both fronto-parietal cortical and subcortical regions and in the basal ganglia (*figure 1C, D*). She received several AED regimens and had a VNS implanted at the age of 14. Currently, she has persistent atypical absence seizures at a variable frequency.

Case 3

A 28-year-old female who had ALL at 4 years of age. Induction and maintenance chemotherapy included prednisone, vincristine, L-asparaginase, MTX, and 6-mercaptopurine. CNS prophylaxis consisted of intrathecal MTX, without cranial radiotherapy. The first seizure occurred at the age of 10. Initially, she was well controlled for several years, but then developed a drug-resistant multifocal epileptic disorder. She had frequent atypical absences and occasional generalized tonic-clonic seizures. Her EEGs showed bilateral independent discharges in both temporal regions and posterior quadrants with frequent bilateral synchrony, and more diffuse or generalized spike-and-wave activity with frontal lobe accentuation. Background activity remained, however, relatively well preserved. Brain MRI and CT scans were unremarkable (*figure 1E, F*). She developed mild intellectual disability with borderline IQ. She received multiple AEDs. At her last follow-up visit, she presented almost daily brief atypical absences and was offered a VNS.

Case 4

A 38-year-old female who had ALL at 4.5 years of age. Induction and maintenance chemotherapy consisted of prednisone, vincristine, 6-mercaptopurine, MTX, and L-asparaginase. CNS prophylaxis consisted of intrathecal MTX and whole-brain radiotherapy. At the age of 15, she started having focal seizures with

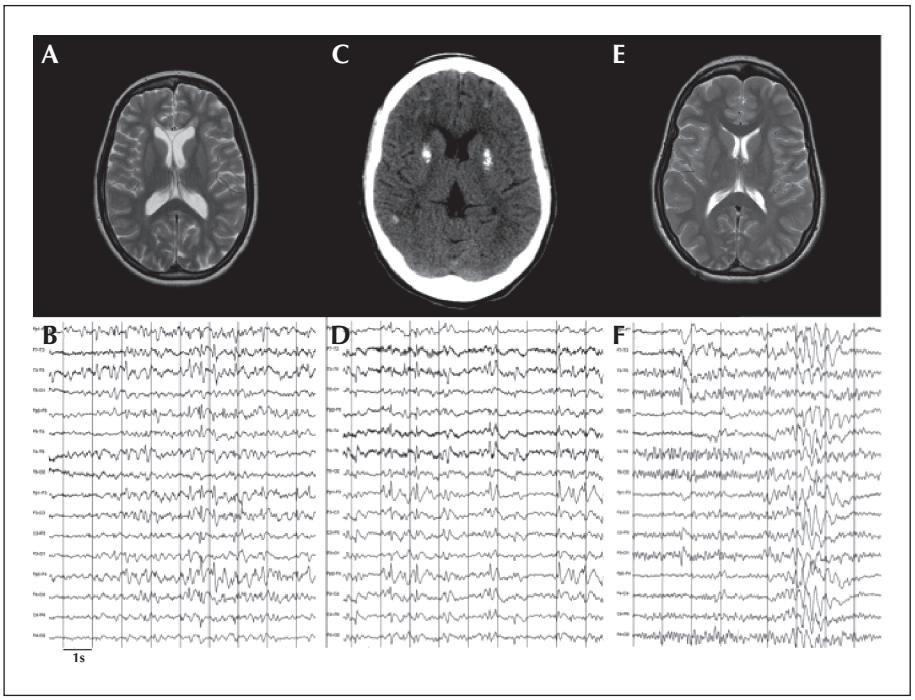

Figure 1. (A, B) Case 1. (A) Axial T2 MRI showing changes consistent with remote anterior callosotomy. No other structural anomalies were seen. Brain CT demonstrated bifrontal cortico-subcortical calcifications (not shown). (B) EEG showing generalized slow spike-and-wave discharges. Background consisted of a 7-8-Hz activity. (C, D) Case 2. (C) Head CT showing calcifications in the basal ganglia bilaterally and at the cortical-subcortical junctions of the frontal and parietal regions. Brain MRI revealed no evidence of leucoencephalopathy (not shown). (D) Interictal EEG showing irregular generalized slow spike-and-wave discharges. Background consisted of a 6-7-Hz activity. (E, F) Case 3. (E) Axial T2 MRI showing no structural abnormalities. (F) EEG showing a left temporal-parietal sharp wave, and a burst of generalized, sharply contoured, slow waves. Background consisted of a 9-10-Hz activity. All EEGs are shown in a "double banana" bipolar montage with a sensitivity of 15 μV/mm.

features suggesting temporal lobe epilepsy. Her EEG revealed a left temporal epileptic focus. Her brain MRI showed a left anterior temporal cavernous angioma (CA), and head CT revealed no calcifications. She was seizure-free for two years with carbamazepine, but then developed drug-resistant epilepsy. She tried vigabatrin, clobazam, and lately lamotrigine without good control of her seizures. She had normal average intellectual functioning. At the age of 21, she underwent a resection of the CA and a left selective amygdalohippocampectomy. She became seizure-free and remained so at her last follow-up visit in 2015. She never experienced symptoms of acute bleeding of the lesion, however, the pathology confirmed the presence of a CA and showed signs of remote bleeding.

Discussion

Central neurotoxicity associated with chemotherapy for the treatment of ALL is well known. MTX is an essential drug in the treatment of this disease, but represents a frequent offender of neurotoxicity. MTX neurotoxicity has been observed after administration of high doses or intrathecal use, and may manifest acutely (hours), subacutely (days to weeks), or in the long term (several years). The neurotoxic effect of MTX is thought to be multifactorial, by a direct toxic effect on astrocytes and axons, and through the interference of the folate pathways. MTX also increases the levels of homocystein, which exerts a toxic effect on the vascular endothelium (Vezmar *et al*., 2003). Furthermore, the combination with cranial radiotherapy has been suggested to intensify intrathecal MTX neurotoxicity. On the other hand, cranial radiation by itself may exert toxic CNS effects; for instance, radiation-induced cognitive impairment, or growth of radiographically occult CA or its *de novo* apparition.

Drug-resistant epilepsy, not associated with acute brain complications or CNS leukaemic involvement, is a rare complication in survivors of ALL. The proposed mechanisms for developing epilepsy have been related to neurotoxicity of intrathecal MTX, brain radiotherapy, or the combination of both therapies. Typically, a variable interval between the ALL treatment and the development of epilepsy has been described, ranging from months to several years (Fasano and Bergen, 2009). Why few individuals develop

Table 1. Demographic, electroclinical, and radiological information.
LGS: Lennox-Gastaut syndrome; TLE: temporal lobe epilepsy. Gen: generalized; GSSW: generalized slow spike and waves; BG: background activity; MTX: methotrexate; IT: intrathecal; 6-MP: 6-mercaptopurine; AEDs: antiepileptic drugs; VNS: vagal nerve stimulator.

Case	Age at ALL Diagnosis (years)	Age at seizure onset (years)	Epilepsy syndrome	EEG findings	IQ	Brain MRI	Head CT	Chemotherapy	Radiotherapy	Epilepsy treatment	Seizure outcome
1	1.5	5	LGS	GSSW, BG 7-8 Hz	Moderate intellectual disability	Unremarkable (following anterior callosotomy)	Bifrontal cortico-subcortical calcifications	Induction and maintenance: prednisone, MTX, cyclophosphamide, vincristine, L-asparaginase; prophylaxis: IT MTX	Yes	Multiple AEDs, ketogenic diet, anterior callosotomy, VNS	Daily seizures
2	2.5	3.5	LGS	GSSW, BG 6-7 Hz	Moderate intellectual disability	Calcifications	Calcifications in both basal ganglia and fronto-parietal cortico-subcortical junctions	Induction and maintenance: MTX and 6-MP; prophylaxis: IT MTX and cytarabine	No	Multiple AEDs, VNS	Weekly seizures

Table 1. (*Continued*)

Case	Age at ALL Diagnosis (years)	Age at seizure onset (years)	Epilepsy syndrome	EEG findings	IQ	Brain MRI	Head CT	Chemotherapy	Radiotherapy	Epilepsy treatment	Seizure outcome
3	4	10	Multifocal epilepsy	Gen with frontal accentuation, and multifocal discharges (max temporal and posterior quadrant) BG 9-10 Hz	Low-average	Unremarkable	No calcifications	Induction chemotherapy: vincristine, MTX and L-asparaginase; maintenance: MTX and 6-MP; prophylaxis: IT MTX.	No	Multiple AEDs	Daily seizures
4	4.5	15	TLE	Left temporal spikes BG 9-10 Hz	Average	Left temporal cavernous angioma	No calcifications	Induction and maintenance: prednisone, vincristine, 6-MP, MTX, L-asparaginase; prophylaxis: IT MTX	Yes	Multiple AEDs, lesionectomy and left amygdalohippocampectomy	Seizure-free

refractory epilepsies while others do not is unknown. Polymorphisms in genes related to neurogenesis represent a possible mechanism recently proposed to explain the susceptibility of MTX-related subacute neurotoxicity in childhood ALL (Bhojwani *et al.*, 2014). This finding suggests that there may be an individual genetic predisposition to develop neurotoxicity after receiving methotrexate. However, there are still no studies describing either a specific genetic predisposition to chronic toxicity or epilepsy in these patients.

Secondary generalized or multifocal epilepsy

Three of our four patients developed drug-resistant epilepsy with intellectual disability, multiple seizure types (atypical absences, and generalized and focal seizures), and multifocal or generalized slow spike-and-wave discharges on the EEG. One had multifocal epilepsy and in two of them the findings were in keeping with Lennox-Gastaut syndrome. The appearance of this syndrome after ALL treatment has been scarcely reported (Mitsufuji *et al.*, 1996; Khan *et al.*, 2003). As was the case in our patients, young age at cancer diagnosis seems to represent a risk factor for developing a severe epileptic encephalopathy (Khan *et al.*, 2003); ALL treatment was given to two patients with LGS-like disorder at 1.5 and 2.5 years old, respectively. This age susceptibility to develop LGS has been hypothesized to be due to increased epileptogenicity in an immature brain during a critical period of cortico-thalamic development (Blume, 2001; Fasano and Bergen, 2009). In patients treated for ALL, the toxic effect of the treatment may increase the cortical excitability and result in spontaneous epileptic discharges. The combination of intrathecal chemotherapy and radiation has been reported to intensify neurotoxicity (Rubinstein *et al.*, 1975). However, the combination of both treatments seems not to be necessary to develop an epileptic encephalopathy (Khan *et al.*, 2003). All of our patients received intrathecal MTX, but only two received concomitant brain radiotherapy.

The majority of the patients who develop LGS after ALL treatment have some evidence of leukoencephalopathy, with or without cortical and subcortical calcifications (Mitsufuji *et al.*, 1996; Fasano and Bergen, 2009). However, leucoencephalopathy can also be seen in asymptomatic children receiving MTX for ALL (Bhojwani *et al.*, 2014). In our small cohort, the two patients with LGS-like disorder presented brain calcifications, but none showed evidence of leucoencephalopathy.

Focal epilepsy

Focal epilepsy is another presentation after ALL treatment. Temporal lobe epilepsy and rare cases of mesial temporal sclerosis have been described (Goyal *et al.*, 2003; Fasano and Bergen, 2009). There are several hypotheses regarding the relationship between antileukaemic treatment and the development of hippocampal sclerosis; chemotherapy may play a role as the initial precipitating factor, and another explanation alleges that radiation-induced damage within the hippocampus leads to sclerosis (Goyal *et al.*, 2003).

As was the case in one of our patients, the appearance of radiotherapy-induced CA is another cause of focal drug-resistant epilepsy in these patients. Cerebral CA is one of the most frequent MRI abnormalities found in leukaemia survivors treated with cranial radiotherapy (Faraci *et al.*, 2011). These angiomas are known to be caused by the release of vascular endothelial factor induced by cranial radiotherapy (Faraci *et al.*, 2011). They also show an increased incidence of spontaneous bleeding when compared to congenital CAs, occurring in up to 40% of the patients (Keezer and Del Maestro, 2009). This has been explained by necrosis and thrombosis of the small vessels induced by radiation. Recurrent microhaemorrhages and haemosiderin deposits in the vicinity of cortical tissue have been proposed to cause hyperexcitability. This associated haemorrhage is highly epileptogenic, and, as shown in our patient, is a complication that often results in refractory epilepsy (Rosenow *et al.*, 2013). Our patient underwent lesionectomy and an ipsilateral selective amygdalohippocampectomy, an approach recommended for patients with dual pathology (Rosenow *et al.*, 2013). In our case, the examination of the surgical specimen confirmed the presence of the CA, showed signs of remote bleeding, but revealed normal mesial temporal structures. As usually described for this kind of lesion, our patient presented an excellent outcome after surgery (Baumann *et al.*, 2007; Rosenow *et al.*, 2013).

In conclusion, drug-resistant epilepsy can be a late complication of ALL treatment that may appear years after the treatment in otherwise asymptomatic individuals. The presentation of epilepsy may vary from focal epilepsy, amenable to surgery, to epileptic encephalopathies such as LGS. It is important to recognise the relationship between the treatment and the development of epilepsy in order to advise about this possible complication and minimise the diagnostic tests that may be necessary to investigate other aetiologies in this group of patients. Nonetheless, this complication remains rare, and individual intrinsic predisposition should be considered. □

Supplementary data.
Supplementary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
The authors have no conflicts of interest to disclose.

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TEST YOURSELF

(1) Is drug-resistant epilepsy after treatment for childhood acute lymphocytic leukaemia (ALL) a frequent entity?

(2) What types of drug-resistant epilepsy syndromes have been described after treatment for childhood ALL?

(3) Which are the main proposed toxic agents responsible for ALL treatment-related neurotoxicity?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".