

Acute neurotoxicity in children treated for acute lymphoblastic leukaemia – a case series and review of literature

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Complications of paediatric acute lymphoblastic leukaemia therapy in a notable number of patients include acute neurotoxicity, which presents most often as cerebrovascular disease, infection or a variety of nonspecific neurologic signs and symptoms, as well as recognizable clinical- radiological syndromes, due to administered chemo- and radiotherapy. Although acute neurological events are rarely fatal, they usually present as emergency situations, often require treatment postponement and modifications, and can be followed by permanent sequelae in the form of epilepsy or cognitive dysfunction. We present three cases of acute neurotoxicity in childhood leukaemia patients treated at our department. Based on clinical presentation, laboratory and radiological findings, these cerebral events were characterized as ischaemia of the brain, posterior reversible encephalopathy syndrome and brain oedema with syndrome of inappropriate secretion of antidiuretic hormone. Timely and appropriate management resulted in complete neurological recovery in all three patients.

Key words: LEUKEMIA, LYMPHOID; CENTRAL NERVOUS SYSTEM; NEUROTOXICITY SYNDROMES

INTRODUCTION

Acute lymphoblastic leukaemia (ALL), the most common childhood malignancy with the overall survival rate of over 80% worldwide, is nowadays considered a curable disease (1). The high cure rates are mainly attributed to rather aggressive, systemic multi-agent chemotherapy, as well as central nervous system (CNS) prophylaxis in the form of intrathecal therapy and radiotherapy, although advances in supportive care have also added greatly to this success. This intensive treatment, however, is not without considerable morbidity. Namely, almost all paediatric patients are faced with an infection at some point of disease course but a few experience less common complications, including acute and chronic neurotoxicity. About 10% of children with ALL are believed to suffer from CNS toxicities during treatment (2). Neurological complications are divided into two main categories, primary involvement of the CNS by leukaemia cells, and secondary, due to leukaemia itself or the treatment (3). Secondary neurological problems can further be categorized as cerebrovascular events, posterior reversible encephalopathy syndrome (PRES), parenchymal atrophy, infection, complica-

tions due to chemo- or radiotherapy, and secondary brain tumours (3). Clinical manifestations vary from headaches, impaired consciousness to seizures and focal motor deficits, and can be quite nonspecific, so accurate diagnosis is made based on medical history, specific laboratory testing, electrophysiological studies and appropriate imaging (4). Standard imaging techniques, including computed tomography (CT) and magnetic resonance imaging (MRI), are indispensable in identifying acute and chronic neurological developments, as well as the possible aetiology (5). Despite appropriate diagnostic and therapeutic approach, more than 30% of affected patients develop permanent sequelae in the form of epi-

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Primljeno/Received: 23. 01. 2020., Prihvaćeno/Accepted: 26. 03. 2020.

TABLE 1. Clinical, diagnostic and therapeutic patients' characteristics

Patient	Case 1	Case 2	Case 3.
Diagnosis	ALL	ALL	ALL- relapse
Risk group	HR	HR	IR
CNS involvement	No	No	No
Protocol phase	ALL IC-BFM 2009 Induction	ALL IC-BFM 2009 Re-induction	ALL-REZ BFM Consolidation
Proximate therapy	Prednisone VCR Daunorubicin L-ASP MTX IT	Dexamethasone VCR Doxorubicin L-ASP MTX IT	Dexamethasone VCR Idarubicin PEG- ASP MTX/Cytarabine/Prednisone IT
Clinical presentation	Epileptic seizure Nystagmus Incoherent speech Hemiparesis	Epileptic seizure Confusion Hallucinations	Epileptic seizure
EEG	Abnormal	Normal	Abnormal
MRI	Ischaemia in the PCA blood supply area	PRES	Cortical oedema Prior leucoencephalopathy
Suspected aetiology	Drug-induced	Hypertension	Electrolyte imbalance (hyponatremia) with prior leucoencephalopathy
Therapy	AET LMWH AHT	AHT AET Antiedematous Electrolyte infusions	AHT AET Antiedematous Electrolyte infusions
Follow-up MRI	Mild cortical atrophy	Residual gliosis	Calcified microangiopathy
Clinical outcome	Complete recovery	Complete recovery	Complete recovery

ALL = acute lymphoblastic leukaemia; CNS = central nervous system; HR = high risk; IR = intermediate risk; VCR = vincristine; L- asp = L-asparaginase; PEG-ASP = pegylated asparaginase; MTX = methotrexate; IT = intrathecal; AET = antiepileptic therapy; LMWH = low molecular weight heparin; AHT = antihypertensive therapy; MRI = magnetic resonance imaging

lepsy or mental retardation, so prompt and proper management is mandatory (6).

CASE REPORTS

We present three children treated for ALL at our institution, who experienced different forms of acute neurotoxicity during intensive chemotherapy. Summary of patient characteristics with clinical data and radiological findings is shown in Table 1.

Case 1

A 7-year-old girl was diagnosed with high-risk ALL, CNS-negative. At the end of ALL IC-BFM protocol induction (prednisone 60 mg/m²/d, vincristine (VCR) 1.5 mg/m²/d, daunorubicin 30 mg/m²/d, L-asparaginase (L-ASP) 5000 IU/m²/d, methotrexate (MTX) 12 mg IT), she suddenly collapsed following an episode of febrile neutropenia and paralytic ileus. Incoherent speech and horizontal nystagmus were observed and high blood pressure recorded. Intravenous diazepam and oral nifedipine were administered, and no further attacks were noted but left arm tremor with hypotonia and adynamia persisted. Urgent brain MRI re-

vealed ischaemia in vascular supply of the posterior cerebral artery (Figure 1), and because of suspected thrombosis anticoagulation therapy (enoxaparin) was initiated. Due to abnormal electroencephalogram (EEG), antiepileptic therapy (levetiracetam, topiramate) was also started. Mild left-sided paresis gradually disappeared leading to full recovery consistent with completely normal brain MRI only one month later.

Case 2

An 8-year-old boy who received chemotherapy according to the ALL IC-BFM protocol for high-risk ALL, CNS-negative, was admitted during re-induction due to febrile neutropenia and electrolyte imbalance. Ten days after the end of the first phase re-induction chemotherapy (dexamethasone 10 mg/m²/d, VCR 1.5 mg/m²/d, doxorubicin 30 mg/m²/d, L-ASP 10000 IU/m²/d), he developed tonic-clonic seizures that were discontinued with parenteral diazepam, while prolonged serum electrolyte imbalance was treated accordingly. Persistent hypertension demanded combined therapy (enalapril, propranolol, furosemide). EEG showed no abnormalities, brain MRI findings were consistent with PRES (Figure 2). Subtle convulsive attacks accompanied by

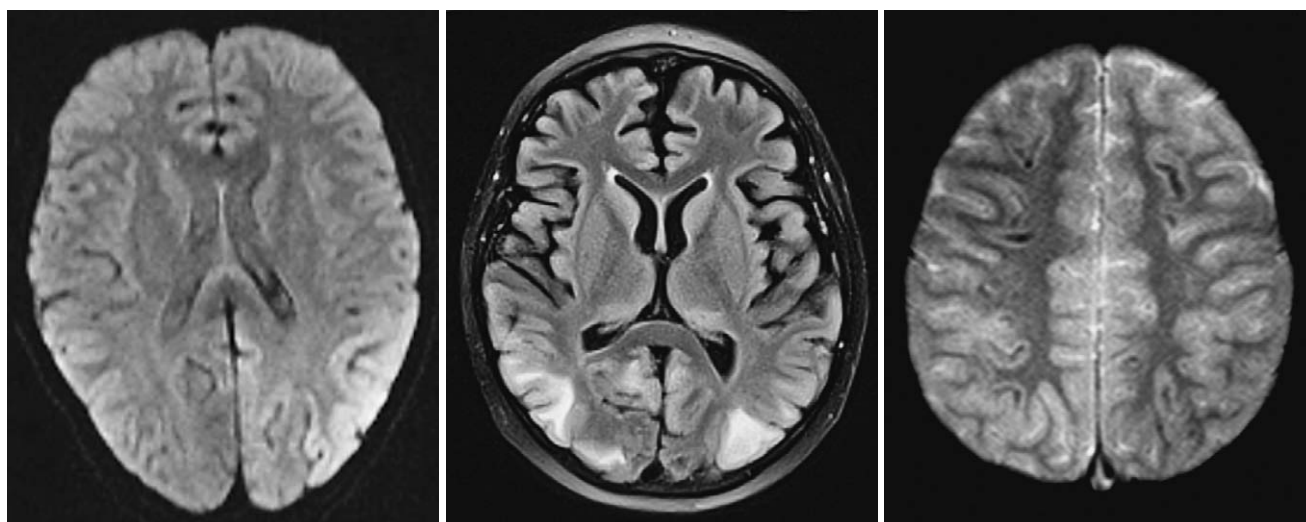


FIGURE 1. MRI findings of the three cases presented: case 1 – ischaemia in vascular supply of the posterior cerebral artery; case 2 – posterior reversible encephalopathy syndrome; case 3 – calcified microangiopathy.

hallucinations and somnolence registered in the next few days were eventually terminated with an antiepileptic (levetiracetam). Slow but complete neurological recovery was observed and brain MRI performed three months later revealed regression of the previous lesion with residual gliosis.

Case 3

A 10-year old girl was treated for late onset, medullary relapse of CNS-negative ALL according to the ALL-REZ BFM protocol. The end-phase of initial leukaemia treatment was complicated by seizures with normal EEG and brain MRI displaying leukoencephalopathy. During the third chemotherapy cycle for relapse (dexamethasone 6 mg/m²/d, VCR 1.5 mg/m²/d, idarubicin 6 mg/m²/d, pegylated asparaginase 1000 IU/m²/d, MTX/Cytarabine/Prednisone 12/30/10 mg intrathecally), she developed two convulsive attacks (munching, head and eye deviation), lasting for a few minutes, half an hour apart. Parenteral midazolam was administered and due to respiratory instability, she was intubated and transferred to the Intensive Care Unit. High blood pressure measurements were recorded repeatedly, while serum electrolytes and glucose tests were initially in the reference range. Antihypertensive (amlodipine) and antiepileptic (levetiracetam, valproic acid) therapy was initiated, while persistent hyponatremia within the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) required ample electrolyte supplementation. Initial brain CT scan appeared to be normal, whereas brain MRI showed posterior segment cortical oedema. Left focal EEG abnormalities were recorded additionally. Later on, the patient experienced seizures on one more occasion, antiepileptic therapy was continued and her neurological status was satisfactory. Follow-up brain MRI three months later revealed calcified microangi-

opathy with glial scarring in the left parietal and right occipital lobe (Figure 3). The girl is now recovering from allogeneic hematopoietic stem cell transplant.

DISCUSSION

Every organ and system can be adversely affected during intensive ALL treatment, but immune and hematologic function, gastrointestinal system with liver function followed by central and peripheral nervous system seem to be damaged most (7). Acute, transient cerebral complications appear in up to 10% of children with ALL (6, 8) and they were the focus of our interest in this paper. The most common acute neurotoxicity includes cerebrovascular events, presenting as cerebral infarcts and venous thrombosis, and infection, mostly meningitis, usually of iatrogenic aetiology (9). According to other published papers, methotrexate-leukoencephalopathy (MLE) was the most frequent neurological syndrome (10). PRES, however, is increasingly more often recognized as the leading acute cerebral complication (6). Metabolic disturbances must also be considered among the main causes of acute CNS disease. These discrepancies in reported frequencies might be a result of diverse categorization of toxic neurological events and different level of health care among countries. None of our cases included infection, but cerebrovascular manifestation, PRES and leukoencephalopathy were evenly represented. The majority of these events ensue during the induction (6, 10). Only in our first patient, the timing was set in the early phase of treatment, suggesting that both consolidation and re-induction could present critical time points for neurotoxic effects of therapy. Seizure is the most common symptom, occurring as an isolated or combined manifestation, followed by focal motor deficit (2, 10), the fact confirmed by all

of our three cases. Although clinical presentations can be rather general and inconclusive, certain neurological events such as PRES and MLE are reproduced in a specific and recognizable clinical-radiological pattern (4). PRES is recognized as a combination of clinical symptoms, including headache, altered mental status, seizures and visual disturbances, accompanied by transient subcortical white matter changes on T2W MRI, reflecting symmetrical vasogenic oedema mostly in the parietal and occipital region. Because hypertension, often of secondary aetiology, is the most significant preceding event, appropriate treatment includes both antiepileptic and antihypertensive therapy. Our male patient had a typical clinical-radiological model of PRES and with immediate and appropriate treatment suggested above, he has recovered completely, an outcome seen in almost 90% of affected patients (11).

Cerebrovascular accident, also referred to as stroke, is the most serious manifestation of cerebrovascular disease and one of the most severe acute neurological events that is broadly classified as hemorrhagic or ischaemic. Acute intracerebral haemorrhage in leukemic patients occurs mainly due to thrombocytopenia, hyperleukocytosis or disseminated intravascular coagulation, while intracranial thromboembolic events are often a result of different chemotherapy agents, including intrathecal therapy (12). Treatment with L-ASP, a drug causing imbalance of the pro- and anti-coagulating systems, is considered a major risk factor for thrombotic events and cerebral sinovenous thrombosis (CSVT), particularly in the early stage of ALL treatment (4). CSVT appears in up to 2% of children and young adults with ALL, it is always symptomatic, and apart from L-ASP, is linked to immobility, infection and dehydration (13). Diagnosis is established by CT, CT or MR angiography, and treatment is based on anticoagulation with intensive supportive care. Our first patient suffered from an ischaemic insult with few symptoms typical for posterior circulation defect (hemiparesis, speech deficit), most probably as a result of L-ASP and concomitant steroid administration, although sepsis might be an additional risk factor.

Methotrexate is another important and indispensable drug in ALL chemotherapy regimen, administered either systemically or intrathecally, known for its acute, subacute and chronic neurotoxicity. The most common complication of intrathecally administered MTX is aseptic meningitis, less often PRES or seizures (14). Acute neurotoxicity takes place within 24 hours of both ways of administration and usually resolves by itself (11). Subacute manifestations occur up to two weeks after drug application and include transitory symptoms such as cerebrovascular insult, encephalopathy or convulsions (15). Postponed complication in the form of leucoencephalopathy, seen as white matter T2 hyperintensity,

arises at least six months after intrathecal MTX therapy, usually is mild and asymptomatic (14). It is almost as frequently described on brain MRI in patients receiving intrathecal MTX as in those treated with cranial irradiation (16). Leucoencephalopathy is a common but often accidental finding at the end of leukaemia treatment and successive intrathecal therapy in many of the symptomatic patients in our institution (study ongoing), as was also the case in relapsed ALL.

The most common electrolytic disturbance in general, and therefore also in paediatric oncology, is hyponatremia, which is usually iatrogenic, caused by SIADH (4). This syndrome occurs as a result of cytotoxic drug administration, such as VCR, cyclophosphamide, melphalan or cisplatin, and is dealt with removal of causative agent, fluid restriction and hypertonic saline (11). All of our patients had hyponatremia that was, however, in two cases mild and was corrected within a few days, and therefore cannot be headlined as the main cause of the neurological events described. On the other hand, the female patient with relapsed ALL had persistently low sodium concentrations as part of SIADH and most probably as a result of VCR therapy, which was later on one-time omitted.

Most of the acute neurological complications in ALL patients during antileukemic therapy present as emergency situations that require rapid identification and intervention. Although half of the patients are found healthy on follow-up, CNS complications are still burdened with rather high morbidity and mortality, as about one-third of patients die or develop permanent consequences (9). Epilepsy is a long-term sequela found in every fifth patient who suffer from acute CNS toxicity, mostly PRES (17). Most deaths due to CNS complications, interestingly, are attributed to intracranial thrombosis (6). Luckily, no lethal outcome was noted in our patients; the more so, complete neurological recovery was the end-result of these three different, yet equally serious cerebral events.

To summarize, CNS manifestations are rather common acute developments in the first few months of ALL therapy, which not infrequently necessitate treatment modifications and have late repercussions, but are rarely fatal. Therefore, accurate diagnosis, prompt treatment and preferably early recognition of risk factors with reasonable prevention is crucial.

Abbreviations:

ALL - Acute lymphoblastic leukemia
 CNS - Central nervous system
 IT - Intrathecal therapy
 PRES - Posterior reversible encephalopathy syndrome
 CT - Computed tomography
 MRI - Magnetic resonance imaging
 VCR - Vincristine

L- ASP - L-asparaginase
 MTX - Methotrexate
 EEG - Electroencefalogram
 SIADH - Syndrome of inappropriate secretion of antidiuretic hormone
 MLE - Methotrexate- leukoencephalopathy
 CSVT - Cerebral sino-venous thrombosis

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SAŽETAK

Akutna neurološka zbivanja u djece liječene od akutne limfoblastične leukemije

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U nezanemarivom broju pedijatrijskih bolesnika s akutnom limfoblastičnom leukemijom komplikacije primijenjene kemoterapije i radioterapije uključuju akutnu neurotoksičnost, koja se može manifestirati kao cerebrovaskularna bolest, infekcija, skup nespecifičnih neuroloških simptoma i znakova, ili pak kao jasno definirani i prepoznatljivi kliničko - radiološki sindrom. Iako akutna neurološka zbivanja rijetko završavaju smrtno, najčešće je ipak riječ o hitnim stanjima koja nerijetko zahtijevaju odgodu ili promjenu terapije te mogu biti praćena trajnim posljedicama, poput epilepsije i kognitivne disfunkcije. Prikazujemo tri slučaja akutne neurotoksičnosti u djece s leukemijom liječene u našem Zavodu. Temeljem kliničke slike, laboratorijskih i radioloških nalaza okarakterizirana su kao moždana ishemija, sindrom posteriorne reverzibilne encefalopatije i edem mozga sa sindromom neadekvatne sekrecije antidiuretskog hormona. Uz pravodobnu i adekvatnu terapiju u sve troje bolesnika zamijećen je potpun neurološki oporavak.

Ključne riječi: LEUKEMIJA, LIMFOBASTIČNA; CENTRALNI NERNVI SISTEM; NEUROTOKSIČNOST