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Original Article

Neurologic toxicity in children with acute lymphoblastic leukemia

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ABSTRACT

Objective: The objective of this study was to evaluate the occurence of neurological complications and long-term neurological sequelae in children with acute lymphoblastic leukemia (ALL). These complications were examined in relation to demographic characteristics, leukemia risk groups, and chemotherapy type.

Material and Methods: A total of 165 patients aged between 1 and 18 years of age who underwent ALL IC-BFM 2009 chemotherapy at the Pediatric Hematology Unit of Ankara Pediatric Hematology and Oncology Research and Training Hospital between June 2013 and December 2018 were retrospectively evaluated.

Results: Forty-two neurological complication episodes (1 to 3 per patient) were observed in 37 (22.4%) patients during chemotherapy. No significant differences between groups with or without neurological complications were detected in terms of age, gender, type of leukemia, risk group assignment, and relapse status (p=0.150, p= 0.170, p= 0.810, p= 0.370, and p=0.340, respectively). Complications were more likely to occur in preB-ALL patients with intermediate to high-risk status, and approximately half of the complications were identified during the early phases of treatment, i.e., induction and early consolidation; also, vincristine, methotrexate, and corticosteroids were more likely to lead to neurotoxicity. The two most common complications included polyneuropathy in 47.6% of the patients and posterior reversible encephalopathy syndrome in 16.7%. Other complications included cranial neuropathy, secondary intracranial hypertension, cortical atrophy, epilepsy, encephalopathy, myopathy, cranial thrombosis, psychotic disorder, and cerebral edema. While none of the neurological complications were associated with mortality, 21.4% of the patients had varying types of sequela, the most common being epilepsy.

Conclusion: Despite increased success rates with intense therapeutic approaches in pediatric ALL patients, 22.4% of this population experienced neurological complications. Long-term follow-up is warranted to evaluate the adverse effects and sequelae of chemotherapy more definitely.

Keywords: Acute lymphoblastic leukemia, Neurologic complications, Polyneuropathy, Posterior reversible encephalopathy syndrome

INTRODUCTION

Acute lymphoblastic leukemia (ALL) comprises one-third of all cancers of childhood and 75% to 80% of all acute leukemias. It occurs more commonly in males, Caucasians, and pediatric patients between 2 and 5 years of age (1). The reported incidence in our country is estimated to be 1.4/100000 (2). Significant variations may exist between ALL patients in terms of clinical and laboratory characteristics, treatment, follow-up, and many disease subtypes have been described. Treatment strategies include different chemotherapy regimens and are based on four basic therapy steps constructed on risk groups and prognostic factors. These treatment steps include remission induction, consolidation for residual leukemia, central nervous system (CNS) eradication, and maintenance. The objectives of the treatment include achievement of remission, prevention of relapses, and eradication of minimal residual disease (MRD). Recently introduced treatments not only have been able to reduce the risk of relapse but also achieved event-free survival rates of up to 85% to 90% (3,4). However, this also led to an increased occurrence of complications caused by early and/or late side effects of such treatments. Early recognition and treatment of these complications are of utmost importance due to associated high morbidity and mortality (5,6). The dosage, route, length of administration, and concomitant use of chemotherapeutic agents are among the important

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determinants of the risk of complications (7,8). While CNS and peripheral nervous system involvement is rare at the time of diagnosis, complications involving both of these nervous systems may occur during ALL treatment. Involvement of the peripheral nervous system is defined as the involvement of any part of the nervous system, including motor neurons, sensory ganglia, nerve roots, plexuses, cranial and peripheral nerves, and neuromuscular connections.

Chemotherapy may cause both peripheral neurotoxicity, consisting mainly of a peripheral neuropathy, and central neurotoxicity, ranging from minor cognitive deficits to encephalopathy. Peripheral neuropathy may be the dose-limiting toxicity, therefore the assessment of peripheral neuropathy and its impact on quality of life should be evaluated during therapy. CNS toxicities such as seizures, drowsiness, cognitive deficits or even coma are observed less frequently. However, these adverse effects should always be taken into account when starting clinical chemotherapeutic trials.

In this study, we aimed to evaluate neurological complications and long-term neurological sequela in a group of pediatric ALL patients receiving ALL IC-BFM 2009.

MATERIALS and METHODS

A total of 165 ALL patients aged between one and 18 years and receiving ALL IC-BFM 2009 protocol at Pediatric Hematology Unit, Ankara Pediatric Hematology and Oncology Research and Training Hospital between June 2013 and December 2018 were retrospectively examined for neurological complications (9).

Risk groups were defined based on BFM ALL IC 2009 protocol; standard risk group (SRG):<1x 10^9 /L blasts on peripheral blood smear on day eight, age between one and six years, initial leukocyte count <20x10^9/L, MRD on day 15<0.1%, and <5% blasts on bone marrow aspirate on day 33; high-risk group (HRG): hypodiploidy or t(9;22) or t(4;11) or more than 1x10^9/L blasts on peripheral blood smear on day 8 or MRD on day 15>10% or more than 5% blasts on bone marrow aspirate on day 33; intermediate-risk group (IRG): patients not stratified as SRG or HRG.

CNS status was defined as CNS-1 (no detectable blast cells in a sample of cerebrospinal fluid), CNS-2 (<5 leukocytes per cubic millimeter with blast cells in a sample with <10 erythrocytes per cubic millimeter), CNS-3 (≥5 leukocytes per cubic millimeter with blast cells in a sample with <10 erythrocytes per cubic millimeter), or traumatic lumbar puncture with blast cells (≥10 erythrocytes per cubic millimeter with blast cells).

Demographic data such as age, gender, age at diagnosis, age at onset of symptoms as well as the type of leukemia, risk group, presence of CNS involvement, relapse/remission status, neurological complications before treatment, concomitant symptoms and signs, phase of chemotherapy at the time of complications, relationship to drugs, comorbid conditions, laboratory results, computed tomography (CT) and magnetic resonance imaging (MRI) findings, and electroencephalography (EEG) and electromyography (EMG) results were retrieved from the electronic database. Exclusion criteria included the presence of leukemias other than acute lymphoblastic leukemia, infant leukemia, follow-up treatments in another center, and bone marrow transplantation.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, New York, USA) was used to analyze the data. Descriptive statistics were presented as frequency, percentage, mean, and standard deviation. The normal distribution of the data was tested with Shapiro-Wilk's test. The difference in age and age at onset of symptoms between patients with or without neurological complications was examined using the Mann-Whitney test, while percentages of demographic characteristics were analyzed with the chi-square test. p value <0.050 was considered statistically significant.

RESULTS

Of the 165 ALL patients included, 97 (58.8%) were male and 68 (41.2%) were female. The medan age at diagnosis was 7.5± 4.5 years (min-max, 1.6-17.7 years). Pre B ALL and T-cell ALL were diagnosed in 144 (87.3%) and 21 (12.7%) of the patients, respectively. There were 13 patients (7.9%) in the standard risk group, 83 patients (50.3%) in the intermediate-risk group; and 69 patients (41.8%) in the high-risk group. One-hundred and forty-eight patients (89.7%) were in remission, while 31 (18.8%) had a relapse during follow-up. Central nervous system involvement (CNS-3) was present in 5/165 patients (3%) at the time of diagnosis. During the study, 42 neurological complications were detected in 37 patients (22.4%) on average at the 7th months of the treatment (min-max, 1-26 months). The mean age of these patients was 8.4±4.7 years and 23 (62.2%) were male.

Of the 37 patients, 31 (83.8%) had a diagnosis of pre B-ALL (21.5% of all pre B-ALL patients), and 35 neurological episodes were identified in these cases. On the other hand, six (16.2%) had a diagnosis of T-ALL (28.5% of all T-ALL patients), and neurologic episodes were detected of them. Both IR and HR patients had 20 episodes each (47.6%), while two complications (4.8%) emerged in SRG patients.

Nine of the patients (24.3%) who developed neurological complications were relapsed ALL. In these patients, neurological complications occurred during relapse treatment in seven (77.8%) and maintenance treatment in two. Two of the patients with neurological complications (5.4%) had leukemic involvement of the CNS at the time of diagnosis. Patients with

Table I: Characteristics of patients

Properties	All patients (n=165)	Neurological Complications		p
		Yes (n=37)	No (n=128)	
Age *(year)	7.5±4.5	8.4±4.7	7.2±4.5	0.150‡
Gender†				0.170§
Male	97 (58.8)	23 (62.2)	74 (57.8)	
Female	68 (41.2)	14 (37.8)	54 (42.2)	
Type of leukemia†				0.810§
Pre B-ALL	144 (87.3)	31 (83.8)	113 (88.3)	
T-ALL	21 (12.7)	6 (16.2)	15 (11.7)	
Risk†				0.370§
SRG	13 (7.9)	2 (5.4)	11 (8.6)	
IRG	83 (50.3)	18 (48.6)	65 (50.8)	
HRG	69 (41.8)	17 (45.9)	52 (40.6)	
Relapse†	31 (18.8)	9 (24.3)	22 (17.2)	0.340§
CNS involvement†				
Yes	5 (3)	2 (5.4)	3 (2.3)	
No	160 (97)	35 (94.6)	125 (97.7)	

***:** *mean*±SD, **†:** *n(%)*,**‡:** *Mann-Whitney test*, **§:** Chi-square test, ***ALL:** acute lymphoblastic leukemia*, ***SRG:** standard risk group*, ***IRG:** intermediate risk group*, ***HRG:** high-risk group*, ***CNS:** central nervous system*

Table II: Neurological complications

Diagnosis	Complication-detected* (n=42)	All ALL patients† (n=165)
Polyneuropathy	18 (42.8)	10.9
PRES	7 (16.7)	4.2
Cranial neuropathy	3 (7.1)	1.8
Myopathy	3 (7.1)	1.8
Secondary intracranial hypertension	3 (7.1)	1.8
Cortical atrophy	2 (4.8)	1.2
Epilepsy	2 (4.8)	1.2
Encephalopathy	1 (2.4)	0.6
Cranial thrombosis	1 (2.4)	0.6
Psychotic disorder	1 (2.4)	0.6
Cerebral edema	1 (2.4)	0.6

***:** *n(%)*,**†:** *%*, ***PRES:** posterior reversible encephalopathy syndrome*

or without neurological complications were not significantly different in terms of age, gender, leukemia type, risk groups, and relapse status (p=0.150, p= 0.170, p= 0.810, p= 0.370, and p=0.340, respectively) (Table I).

There was a total of 22 patients (13.3%) who had muscle weakness, gait impairment, leg pain, and loss of deep tendon reflexes. Motor and/or sensory axonal polyneuropathy (PNP) was diagnosed in 14 patients based on EMG assessment, and in 4 patients based on clinical findings (n=18; 10.9%); in all of these cases, the event was considered associated with vincristine (VCR) treatment. Three patients have one or more of neuropathic symptoms and signs, three patients were diagnosed steroid-related myopathy and one patient was diagnosed intrathecal MTX-related cytotoxic cerebral edema.

Of the patients with polyneuropathy, 83.3% had pre B-ALL with 50% diagnosed in induction, 16.7% in reinduction, and 5.5% in HR consolidation. All of these protocol phases included use of Vincristine and Prednisone/dexamethasone.

Following the emergence of the complications, treatment consisting of B-vitamin complex and gabapentin was given. Three patients (1.8%) developed neuropathic pain and one (0.6%) had dropped leg as a sequela. In three patients (1.8%) cranial neuropathy was present. Autonomic neuropathy symptoms such as constipation could not be retrieved from patients' records due to missing data. There were 11 patients (6.7%) who had convulsions, in association with headache, visual and speech impairment, altered consciousness, and loss of muscle strength. In seven patients (4.2%), a cranial MRI was performed, and posterior reversible encephalopathy syndrome (PRES) was diagnosed. In four other patients with convulsions, sinus venous thrombosis, encephalopathy, and epileptic activity were detected. Six (85.7%) of the patients with PRES had pre B-ALL, and five (71.4%) had HR status and received induction, reinduction, HR block, and relapse treatments. Six (85.7%) had hypertension, and two (28.6%) had hyponatremia at the time of the episode. Following the occurrence of the complications, appropriate antiepileptics, antihypertensives, and sodium replacement were given to symptoms and comorbidities. Of the patients with PRES, three (42.8%) had epileptic sequela. Table II shows all neurological complications.

In a patient (0.6%) in the IR group aged 16.6 years and diagnosed with pre B-ALL, a cranial MRI was performed due to headache, convulsion, and loss of motor strength during induction treatment revealed hemorrhage; also, venography showed sinus venous thrombosis which was thought to be associated with steroids and L-asparaginase given during induction. Low molecular weight heparin at a dose of 100 U/kg BID was administered for one month, followed by once-daily administration for six months. Thrombosis was completely

Table III: Summary of clinical, radiographic and electrophysiological findings

Leukemia Type	Risk/Patient number	Age (year)	Protocol	Symptoms	Signs	Eye Exam	EEG	EMG	CT	MRI	LP	MR Venography	Diagnosis	Treatment	Sequela
PreB-ALL	SRG 1	4.5	PIA	Walking disorder	DTR loss			None					PNP	B-vit complex	
	2	3.6	PIB	Walking disorder	DTR loss- Loss of strength			None		N			Myopati	B-vit complex	
	IRG 3	3.1	PIA	Walking disorder	Loss of strength			None					PNP	B-vit complex	
	4	10.2	PIA	Seizure	Confusion		Encephalopathy		Cortical atrophy	PRES			PRES	Antihypertensive + Antiepileptic	Epilepsy
	5	4.5	PIA	Seizure	Confusion		Cerebral disfunction			PRES			PRES	Antihypertensive + Antiepileptic	Epilepsy
	6	4.2	PIA	Weakness	DTR loss			Motor axonal PNP					PNP	B-vit complex + Gabapentin	
	7	14.5	PIA	Weakness- Walking disorder	DTR loss			Motor axonal PNP					PNP	B-vit complex + Gabapentin	
	8	16.6	PIA	Seizure- Headache	Loss of strength	N				Subdural hemorrhage	Sagittal sinüs thrombosis		Cranial thrombosis	Antiepileptic + LMWH	
		17	PII-faz1	Aggression	None	N				N			Psychotic disorder	Antipsychotic	
	9	3.3	PM	Weakness- Walking disorder	Loss of strength			Motor axonal PNP		N			PNP	B-vit complex + Gabapentin	
	10	12.2	PIB	Headache	None					N	Increased CSF pressure		Secondary intracranial hypertension	Acetazolamide	
	11	6.5	PIB	Weakness- Walking disorder	DTR loss			Motor axonal PNP		Cortical atrophy			PNP	B-vit complex + Gabapentin	
	12	5.8	PIB	Walking disorder	None			None					Myopati	B-vit complex	
	13	3.9	PIB	Weakness- Walking disorder	DTR loss			None					Myopati	B-vit complex	
		6.9	Relaps	Ptosis	Myosis	Myosis, Ptosis				N			Cranial neuropathy	Gabapentin	
PreB-ALL	IRG 14	16.7	PII-faz1	Weakness- leg pain	DTR loss- Loss of strength			Motor axonal PNP		N			PNP	B-vit complex + Gabapentin	Neuropathic pain
	15	4.9	PII-faz1	Weakness- Walking disorder	DTR loss			Motor axonal PNP					PNP	B-vit complex + Gabapentin	
	16	11.3	PII-faz2	Weakness	Loss of strength				N	Cytotoxic edema		N	Cerebral edema		
	17	10.4	Relapse	Headache- Vomting	None	N				N	Increased CSF pressure		Secondary intracranial hypertension	Acetazolamide	
	18	15.9	Relapse	Drooping of the mouth	Cranial nerve paralysis- hemiplegia					Restricted diffusion		N	Cranial neuropathy		
	HRG 19	6.6	PIA	Weakness- leg pain- Walking disorder	DTR loss- Loss of strength			Motor axonal PNP					PNP	B-vit complex + Gabapentin	

Leukemia Type	Risk/Patient number	Age (year)	Protocol	Symptoms	Signs	Eye Exam	EEG	EMG	CT	MRI	LP	MR Venography	Diagnosis	Treatment	Sequela
PreB-ALL	20	11.9	PIA	Weakness- Walking disorder	DTR loss- Loss of strength			Motor axonal PNP					PNP	B-vit complex + Gabapentin	Drop foot
	21	2	PIA	Walking disorder	None			Motor axonal PNP					PNP	B-vit complex + Gabapentin	
	22	3.1	PIA	Ptosis	Cranial nerve paralysis	Left eye ptosis				N			Cranial neuropathy		
	23	6.6	PIA	Weakness- leg pain	DTR loss			Motor axonal PNP		N			PNP	B-vit complex + Gabapentin	
	24	6.8	PIB	Weakness- Walking disorder	Loss of strength			Motor axonal PNP		N			PNP	B-vit complex + Gabapentin	
	25	12.6	PII-faz2	Seizure	Confusion				N	PRES		N	PRES	Antiepileptic	Epilepsy
	26	15.1	1.HR1	Seizure- Headache	Confusion		N		N	PRES			PRES	Antihypertensive + Antiepileptic	
	27	5.9	2.HR1	Seizure	Confusion		N			PRES			PRES	Antihypertensive + Antiepileptic	
PreB-ALL	HRG 28	17.1	2.HR2	Seizure- Dysarthria	Confusion	N	Cerebral disfunction- Epileptic activity			Cerebral-cerebellar atrophy			Atrophy	Antiepileptic	
		17.1	2.HR2	Weakness- Tremor	DTR loss-dismetri			Bilateral sensorimotor PNP		Cerebral-cerebellar atrophy			PNP	B-vit complex + Gabapentin	Neuropathic pain
		17.2	2.HR3	Seizure	None	N	Epileptic activity		N	Cerebral-cerebellar atrophy			Epilepsy	Antiepileptic	Epilepsy
	29	9.6	Relapse	Headache- Vomiting- Seizure	Confusion					PRES			PRES	Antihypertensive + Antiepileptic	
	30	6.1	Maintenance	Seizure	Confusion		N		Cortical atrophy	N		N	Atrophy		
	31	15.3	Meintenance	Weakness- leg pain	None			None					PNP	B-vit complex + Gabapentin	Neuropathic pain
T-ALL	IRG 1	3.2	PIA	Weakness- Walking disorder	DTR loss			None					PNP	B-vit complex + Gabapentin	
	2	16.2	Relapse	Headache- Speech disorder	None		Epileptic activity			N			Epilepsy	Antiepileptic	Epilepsy
	HRG 3	9.8	PIA	Seizure – Vision problem	Confusion		Abnormal background activity			N			Encephalopathy	Antihypertensive + Antiepileptic	
	4	14.3	PII-faz1	Weakness- leg pain- Walking disorder	DTR loss- Loss of strength- Numbness			Bilateral sensorimotor PNP					PNP	B-vit complex + Gabapentin	
		15.1	Relapse	Seizure	Confusion	N			N	PRES			PRES	Antihypertensive + Antiepileptic	
	5	14.6	PII-faz1	Weakness- Walking disorder	Gowers's sign			Motor axonal PNP					PNP	B-vit complex + Gabapentin	
	6	4	Relapse	Vision Loss	None	Papil edema			N	N	Increased CSF pressure		Secondary intracranial hypertension	Acetazolamide	

EEG: *electroencephalography,* ***EMG:*** *electromyography,* ***CT:*** *computed tomography,* ***MRI:*** *magnetic resonance imaging,* ***LP:*** *lumbar puncture,* ***PreB-ALL:*** *precursor B cell acut lymphoblastic leukemia,* ***T-ALL:****T cell acut lymphoblastic leukemia,* ***IRG:*** *intermediate risk group,* ***HRG:*** *high risk group,* ***PIA:*** *protocol IA,* ***DTR:****deep tendon reflex,* ***PNP:*** *polyneuropathy,* ***PRES:*** *posterior reversible encephalopathy syndrome,* ***CSF:*** *cerebrospinal fluid,* ***B-vit:*** *B-vitamin,* ***N:*** *normal*

resolved with no sequela. The same patient exhibited aggressive behavior during reinduction treatment, although his cranial imaging studies were unremarkable. In consultation with pediatric psychiatry, a diagnosis of steroid-associated psychotic disorder was made. Anti-psychotic treatment was given and the patient recovered without sequela.

Sudden visual loss was seen in three patients (1.8%) (2 of them were pre B-ALL in the IR group and the other patient was T-ALL in the HR group). These patients' cranial imaging showed normal findings, although a lumber puncture indicated increased cerebrospinal fluid pressure. Thus, these patients were diagnosed with secondary intracranial hypertension. These patients recovered fully with acetazolamide treatment. Chemotherapy protocol was modified in seven patients after neurological complications. In three patients (one patient with sinus venous thrombosis, and the other two with PNP), chemotherapy was suspended for one week; in two patients, (one with convulsions and PRES, another with PNP) chemotherapy was maintained with dose reduction; in two patients diagnosed with PNP, vincristine dose was skipped until the next chemotherapy course. Clinical, radiographic and electrophysiological findings of patients are summarized in Table III.

DISCUSSION

Neurological side effects in pediatric ALL patients were detected as 22.4%. Of these, 11.5% and 10.9% affected the CNS and peripheral nervous system, respectively. In several previous studies, the respective figures range between six to 11% and 18 to 50% (10,11). Ethnicity, genetic factors, age, gender, and obesity may account for some of these differences in the reported rates of incidence (16).

In the current study, most of the patients with neurological complications had HR or IR status, and side effects mostly occurred during induction and early consolidation. Baytan et al. (10), administering a very similar chemotherapy protocol to ours (i.e. ALL-BFM 2000), observed neurological complications in 65.2% of the patients in the IR group, and 56.5% of the patients receiving induction treatmet. On the other hand, Aytaç et al. (13) found a neurological complication rate of 60% in HR patients receiving St. Jude's total XI and XIII protocol. In our study, 18 patients (10.9%) were diagnosed with motor and/or sensory axonal polyneuropathy. Of the cases with polyneuropathy, 66.7% were associated with VCR used in induction and early consolidation phases. It appears that incidence may vary according to age, gender, ethnicity, obesity, malnutrition, and genetic polymorphism. The TT (rs924607) genotype of CEP72, a gene involved in microtubule formation; C > T (rs3784867) variation of ABCC1 gene; ABCC2 GG (rs3740066) and GG (rs12826) genotypes; and all homozygous mutant alleles of SLC5A7 gene are associated with reduced CYP3A4 and CYP3A5 enzyme functions, with a consequent increase in the risk of vincristine related neuropathy (14,15). We did not examine any of our patients' polymorphisms associated with VCR neuropathy. The mean age of patients with polyneuropathy was comparable with the overall group of patients with neurological complications, and there were no significant gender differences (55% male). Three patients (1.8%) had cranial neuropathy. No information could be collected from patient files in terms of the development of autonomic neuropathy. As opposed to peripheral or cranial neuropathy, the common occurrence of more general symptoms such as constipation and abdominal pain in patients with autonomic neuropathy may lead to the underdiagnosis of this condition. Clinicians should have a higher index of suspicion for autonomic symptoms when assessing patients with possible neuropathy.

Peripheral neuropathy may be confused with pathological signs of myopathy. Muscle weakness and/or gait disorder could not be related to vincristine use in three of our patients (1.8%), and a diagnosis of myopathy associated with steroid use was made. A routine physical exercise program may have a protective role against the future development of muscular atrophy or joint problems (16).

Seven patients (4.2%) with seizures were diagnosed with PRES, and 5 of these (71.4%) had a high-risk status. Patients were receiving induction, consolidation, re-induction, and relapse treatments, and seizures were probably related to intrathecal MTX or corticosteroids. Six patients (85.7%) had hypertension, and two (28.6) had hyponatremia at the time of the seizure. In the Baytan study, the incidence of PRES was 4.8%, with a higher frequency in HR patients (17). In a multi-center study by Bilir et al. (18), 84.4% of the 58 patients with PRES also had concomitant hypertension. In studies by Tang et al. (19) hypertension was reported to occur in 36.4% of the patients, respectively. Furthermore, it has also been proposed that intravascular hypotonicity due to hyponatremia may lead to extravasation, which then may enter astrocytes through water channels such as aquaporin-4 and may result in cranial edema, as a part of the pathogenesis of PRES (20). In our study, epilepsy as a sequela of PRES was observed in three of the patients (42.4%) diagnosed with PRES. This is consistent with previous reports suggesting that PRES developing during leukemia treatment may be irreversible or may result in epileptic sequela (19).

One of our patients (0.6%) had bleeding and sinus venous thrombosis. The reported incidence of thrombosis developing during treatment of pediatric ALL varies between 1% and 37%, depending on the populations and therapeutic regimens examined. Sinus venous thrombosis represents one of the highest-risk areas of involvement, as it is associated with long term neurologic effects and a high mortality rate of 8% to 13% (21). Risk factors for thrombosis included T cell phenotype, older age, and high-risk status. In other studies, intensive chemotherapy regimens involving long-term exposure to

L-asparaginase and steroids appeared to be associated with the highest risk of thrombosis (22). In our patient, thrombosis was observed during induction treatment and was thought to be associated with L-asparaginase administered during that treatment. L-asparaginase increases the risk of thrombosis and bleeding via decreased hepatic synthesis of fibrinogen and anti-thrombin. Particular attention to L-asparaginase treatment and thrombosis should be paid in pediatric patients since these are directly linked with the course of leukemia and survival (23). Our patient who had a thrombotic event developed the steroid-associated psychotic disorder in the subsequent course of chemotherapy. Treatment with an anti-psychotic agent resulted in full recovery.

Three patients (1.8%) in our study were diagnosed with secondary intracranial hypertension, which is a rare condition in the general pediatric population, with a reported incidence of 0.32/100.000 in the US (24). Several studies involving patients with hematological malignancies have found that certain medications including methotrexate, cytarabine, and all trans-retinoic acid may be associated with symptoms of increased intracranial pressure (25). Similarly, in our patients, increased intracranial pressure developed during early consolidation and relapse treatments, which included methotrexate, and cytosine-arabinoside. In Garcia et al. (26) study comparing increased intracranial pressure syndromes among pediatric leukemia patients, headache and papilledema were present in 90% and 25% of the patients at the time of diagnosis, respectively. Similarly, two of our patients had a headache, and one had a sudden loss of vision. Treatment with acetazolamide resulted in full recovery in all cases.

In conclusion, during the treatment of ALL, a total of 22.4% of neurological complications were detected, of which 11.5% were CNS and the most common was PNP. In 21.4% of these cases, long-term sequela such as epilepsy, neuropathic pain, and foot drop was observed. Potential limitations of our study include its retrospective nature, missing data in patient files, absence of accurate data on the relationship between complications and chemotherapy agents, and lack of routine use of EMG in all patients. Larger and prospective studies may allow better identification of side effects of a wide range of chemotherapeutic agents, in addition to providing further insights into pathophysiologic mechanisms and/or genetic factors for such effects. This may allow the prevention of complications with the use of non-invasive tests or relevant genetic techniques; also, appropriate management strategies against such complications may be developed to achieve sequela-free survival.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by the institutional ethics committee of the Ankara Child Health and Disease Hematology-Oncology Training and Research Hospital (date: 08.04.2019, number: 2019/080).

Contribution of the authors

Özcan AS, Yaralı N: Concept, ***Özcan As, Yaralı Ny:*** Design, ***Özcan AS, Yaralı NY, Akçabelen Ym:*** Supervision, ***Özcan AS, Işık M:*** Data Collection, ***Özcan As, Koca Yozgat A, Akçabelen YM***: Analysis And/Or Interpretation, ***Özcan AS, Koca Yozgat A, Yaralı N:*** Literature Review, ***Özcan AS, Yaralı N:*** Writing, ***Özbek NY Yaralı N:*** Critical Review, ***Özcan AS, Yaralı N:*** References And Fundings, ***Özcan AS, Koca Yozgat A:*** Materials

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Conflict of interest

The authors declare that there is no conflict of interest.

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