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Neurological Complications in Children With Cancer: Experience From a Single Center in Türkiye

Leyla Kara,[1] Ekrem Unal,[2] Huseyin Per,[3] Sefer Kumandas,[3] Mehmet Canpolat,[3] Ferhan Elmali,[4] Alper Ozcan,[2] Ebru Yilmaz,[2] Musa Karakukcu,[3] Mehmet Akif Ozdemir,[2] Turkan Patiroglu,[2] Hakan Gumus[3]

[1]Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[2]Division of Pediatric Hematology and Oncology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[3]Division of Pediatric Neurology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
[4]Department of Bioistatistics, Erciyes University Faculty of Medicine, Kayseri, Türkiye

ABSTRACT

Objective: This study aimed to determine the neurological complications, etiological factors, and sequelae in children with cancer.

Materials and Methods: This retrospective study examined the etiological factors, treatments, and outcomes of neurological complications in 794 children diagnosed with cancer at Erciyes University Faculty of Medicine.

Results: The average age of the participants was 6.8 years (mean 6.8±4.8 years), including 448 (56.4%) boys, and 346 (43.6%) girls. A total of 506 neurological complications were identified in 313 children (39.4%). The most common neurological complications were walking difficulties, headaches, convulsions, and disorders affecting strength, vision, and hearing. The rate of neurological complications was 26.6% among patients with acute lymphoblastic leukemia, with no significant association found between risk groups and the occurrence of neurological complications. However, a significant relationship was observed between neurological complications and increased mortality.

Conclusion: The rate of neurological complications was found to be higher in patients with non-Hodgkin lymphoma (NHL) compared to those with Hodgkin lymphoma (HL). Neurological complications emerge as a risk factor for mortality among children with systemic cancer.

Keywords: Childhood, neurological complication.

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Address for correspondence:
Hakan Gumus.
Division of Pediatric Neurology, Department of Pediatrics, Erciyes University Faculty of Medicine, Kayseri, Türkiye
Phone: +90 352 437 49 10
E-mail: hakgumus@erciyes.edu.tr

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INTRODUCTION

Over the past two decades, the survival rates for childhood cancers have significantly increased, thanks to intensive treatment models. However, these treatments, alongside the disease itself, often lead to systemic side effects in affected children. It is estimated that 75% of survivors face

at least one health issue, with 25% suffering from severe complications that detrimentally impact their quality of life. Numerous effects of cancer are documented, including cardiological, endocrinological, neurological, respiratory, nephrological complications, and secondary cancers.[1]

Cancer-related neurological complications can occur at the time of diagnosis and throughout the course of the disease. It is crucial that neurological complications are diagnosed early and accurately to prevent their progression and the ensuing disability. While studies on neurological complications have been conducted in adult cancer patients, research in children is limited.[2]

Therefore, in this report, we aim to explore the common neurological complications of cancer, including those arising from cancer treatments and paraneoplastic syndromes (e.g., chemotherapy, radiotherapy).

MATERIALS AND METHODS

This study retrospectively evaluated the neurological complications, incidence, etiology, treatment, and prognosis of 794 patients who were followed up at the Erciyes University Pediatrics Hematology-Oncology Clinic between January 2005 and August 2015.

The study received approval from the Pediatric Health and Diseases Division Academic Committee Study Protocol at Erciyes University. It was also submitted to the Local Ethics Committee of Erciyes University and approved on July 24, 2015, under the protocol number 2015-327.

Tumor groups included in the study were leukemias, lymphomas, central nervous system (CNS) tumors, sympathetic nervous system tumors, retinoblastoma, liver, kidney, bone tumors, gonadal and germ cell tumors, soft tissue sarcomas, epithelial tumors, and other unclassifiable malignancies (e.g., Langerhans cell histiocytosis). Neurological complications were determined by evaluating the patients' histories, physical examinations, and laboratory and radiological findings retrospectively from patient records.

Age, gender, diagnosis, initial diagnosis, treatments (including chemotherapy, intrathecal chemotherapy, radiotherapy (RT), hematopoietic stem cell transplant (HSCT), and surgery), chemotherapeutic medications, neurological findings, and sequelae were listed. The causes of the neurological findings and their treatments were investigated. Neurological findings included weakness, headaches, convulsions, sensory dysfunction, tremors, altered mental status, visual dysfunction, hearing loss, speech dysfunction, facial paralysis, intellectual disability, and other rare complications evaluated in the study.

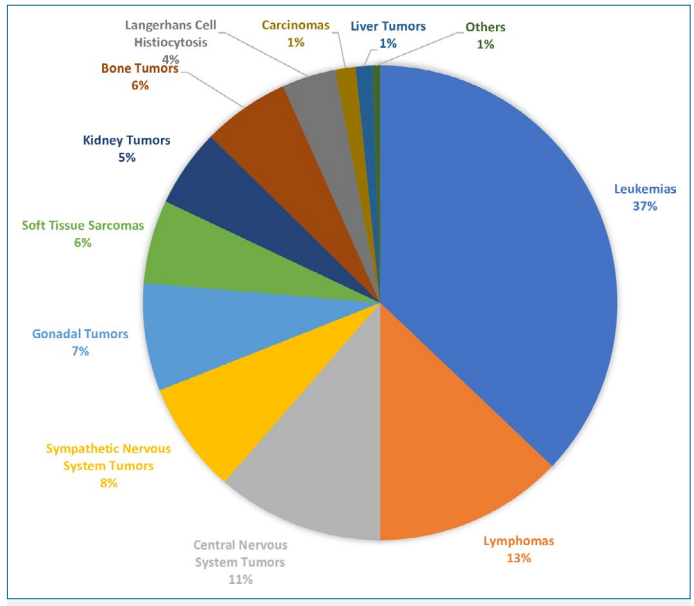

Figure 1. Tumor groups.

The relationship between neurological complications and mortality was analyzed. Data were evaluated using the IBM Statistical Package for the Social Sciences (SPSS) Statistics 22.0 (IBM Corp., Armonk, New York, USA). Descriptive statistics included the number of units (n) and percentage (%). For numerical variables, data adhering to normal distribution parameters were given as standard deviation, and for non-normally distributed data, as median (minimum–maximum). The relationship between categorical variables was examined using the exact method of the Chi-Square test. A p-value <0.05 was considered statistically significant. Continuous variables were compared using a t-test or Mann-Whitney U-test, depending on the normality of distribution. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI).

The sample size; 95% confidence (1-α), 87% test power (1-β), effect size of 0.10 (small according to Cohen's effect size), and the number of samples to be taken according to priori power analysis was determined as 793 patients. Seven hundred ninety four patients could be included in the study.

RESULTS

The median age of the patients was 5.9 years (range: 2.6–10.9). Of the 794 patients who participated in the study, 448 (56.4%) were male, and 346 (43.6%) were female. Among the 794 patients, 293 (36.9%) had leukemia, 102 (12.8%) had lymphoma, 90 (11.3%) had a CNS tumor, 60 (7.6%) had a sympathetic nervous system tumor, 58 (7.3%) had a gonadal tumor, 45 (5.6%) had soft tissue sarcoma, 42 (5.2%) had a kidney tumor, 47 (5.9%)

Table 1. Neurological findings in patients

Neurological findings	Number of cases (n=313)	Percentage (%)
Gait abnormalities	99	19.5
Headache	86	16.9
Seizure	63	12.4
Weakness (Hemiparesis (n=38), Paraparesis (n=7))	45	8.8
Visual dysfunction (visual loss, blurred vision, diplopia)	31	6.1
Hearing loss	22	4.3
Limb pain	22	4.3
Facial paralysis	21	4.1
Abnormal eye movements (nystagmus, strabismus, Horner syndrome, opsoclonus)	21	4.1
Speech dysfunction	16	3.1
Altered mental status	14	2.7
Ptosis	14	2.7
Sensory dysfunction	12	2.3
Backache	7	1.4
Dizziness	7	1.4
Difficulty swallowing	9	1.7
Hallucination (psychosis)	6	1.2
Tremor	3	0.6
Ataxia	3	0.6
Intellectual disability	2	0.4
Chorea	1	0.1
Bulging fontanelle	1	0.1
Depression	1	0.1
Total	506	100

had a bone tumor, 29 (3.6%) had Langerhans cell histiocytosis (LCH), 11 (1.3%) had carcinoma, 9 (1.1%) had a liver tumor, and 8 (1%) had other tumors. Of the 293 patients with leukemia, 221 had acute myeloblastic leukemia, 51 had acute myeloid leukemia, and 21 had other types of leukemia (e.g., chronic myeloid leukemia, biphenotypic leukemia). The distribution of underlying malignancies is described in Figure 1.

Neurological complications were detected in at least one instance in 313 (39.4%) patients. A total of 506 neurological findings were recorded in these 313 patients, averaging 1.6 findings per person (Table 1).

Table 2. Neurological complications in patients with ALL

Causes	Number of cases (n=106)	Percentage (%)
Toxicity of medications		
Vincristine neuropathy	41	38.6
Methotrexate encephalopathy (posterior reversible encephalopathy syndrome)	12	11.3
Steroid-induced osteopenia/myopathy	3	2.8
Infectious complications		
Sinusitis	2	1.8
Brain abscess	1	0.9
Complications of coagulopathy		
Cerebrovascular accident (thrombosis, intracranial hemorrhage) (due to L-asparaginase in 11 patients)	11	10.3
Leukemic involvement	9	8.4
CNS involvement	15	14.1
Idiopathic	9	8.4
Headache after lumbar puncture (LP)	2	1.8
Depression	1	0.9

ALL: Acute lymphoblastic leukemia; CNS: Central nervous system.

Neurologic complications occurred in 106 of the 221 patients with acute lymphoblastic leukemia (ALL) (48%) (Table 2).

According to the Berlin Frankfurt Münster (BFM) protocol, ALL patients were classified into risk groups (SRG: standard-risk group, MRG: medium-risk group, HRG: high-risk group). There was no relationship between neurological complications and risk groups in ALL patients (p=0.509) (Table 3). The rate of neurological complications was higher in patients with CNS tumors compared to those with other tumors (94%), including headaches (43 patients), gait abnormalities (24 patients), seizures (18 patients), visual dysfunction (16 patients), abnormal eye movements (12 patients), speech dysfunction (11 patients), weakness (11 patients), facial paralysis (10 patients), ataxia (9 patients), hearing loss (8 patients), altered mental status (5 patients), and other complications (13 patients). Other complications included difficulty swallowing, chorea, intellectual disability, encephalopathy, dizziness, and back pain.

Neurological complications were detected in 20 of the 102 lymphoma patients. Four patients with stage 1 lymphoma had no neurological complications. There was no relationship between the stage of lymphoma and neurological

Table 3. Relationship between ALL risk group and neurological complications

	Neurological complications group (n=109) (%)	None neurological complications group (n=112) (%)	Total (N=221)	p
SRG	31 (28.4)	26 (23.2)	57	
MRG	64 (58.7)	59 (52.6)	123	0.509
HRG	14 (12.8)	27 (24.1)	41	

ALL: Acute lymphoblastic leukemia; SRG: Standard risk group; MRG: Medium risk group; HRG: High risk group.

complications (p=0.251) (Table 4). The rate of neurological complications was higher in non-Hodgkin lymphoma (NHL) compared to Hodgkin lymphoma (HL) (30% vs. 9.8%).

Headaches are the most common presenting symptom in children with space-occupying intracranial lesions. The causes of headaches included cranial masses (52 patients), metastasis (8 patients), cerebrovascular diseases (6 patients), psychogenic factors (6 patients), infections (e.g., meningitis, mastoiditis, encephalitis, sinusitis) in 6 patients, cerebral hypotension syndrome (post-lumbar puncture syndrome) in 6 patients, and side effects from treatment with all-trans retinoic acid and steroids (2 patients), totaling 86 patients. Six of the 338 patients (1.7%) who underwent a lumbar puncture experienced headaches. Cranial computed tomography and/or cranial magnetic resonance imaging were performed in 81 patients, with cranial magnetic resonance imaging being diagnostic in 82% of cases.

Sixty-three patients experienced seizures, including simple partial, secondarily generalized, complex partial, myoclonic, and tonic seizures. Antiseizure medications used were phenytoin (5 patients), levetiracetam (17 patients), phenobarbital (12 patients), sodium valproate (9 patients), carbamazepine (6 patients), oxcarbamazepine (4 patients), topiramate (1 patient), and others (5 patients). Other antiseizure medications included primidone, clonazepam, clobazam, sultiam, and midazolam. The duration of antiseizure drug use ranged from 0.1 to 84 months, with a mean of 16.6 months. The rate of convulsions was higher in patients who died than in those who survived (p<0.001) (Table 5).

Altered mental status in our patients was due to new or worsening intracranial disease (six patients), posterior reversible encephalopathy syndrome (PRES) (two patients), intracranial hemorrhage or thrombosis (four patients), and leptomeningeal leukemic involvement.

Table 4. Relationship between neurological complications and tumor stage in lymphoma

	Neurological complications group (n=18) (%)	None neurological complications group (n=72) (%)	Total (N=90)	p
Stage 2	8 (44.4)	19 (26.3)	27	
Stage 3	7 (38.8)	43 (59.7)	50	0.251
Stage 4	3 (16.6)	10 (13.8)	13	

Table 5. Relationship between convulsion and mortality in all patients

	Convulsion group (n=44) (%)	None convulsion croup (n=537) (%)	Total (N=581)	p
Survivor	27 (61.3)	453 (84.3)	480 (82.6)	<0.001
Deceased	17 (38.6)	84 (15.6)	101 (17.3)	

Abnormal eye movements, nystagmus, strabismus, right-to-left vision limitations, decreased eye movements, and Horner syndrome were observed. Horner syndrome developed in a patient with stage 4 thoracic neuroblastoma. Abnormal eye movements were caused by CNS tumors in 16 patients.

Sixteen of the 311 patients who received methotrexate (intrathecal and/or parenteral) experienced complications related to methotrexate. In 79 of the 504 patients (15%) who received vincristine, at least one instance of vincristine neuropathy was detected. Observed symptoms included altered gait (54 patients), weakness (15 patients), sensory dysfunction (12 patients) (pain, numbness, tingling), and ptosis (6 patients).

Seventy-five of the 79 patients with neuropathy received medical treatment, including thiamine (62 patients), pyridoxine (68 patients), pyridostigmine (29 patients), and gabapentin (4 patients).

Hearing loss due to cisplatin was detected in 13 of the 138 patients (9%) who received cisplatin. Cerebrovascular events due to L-asparaginase developed in 11 of the 235 patients (4%) who received L-asparaginase. A convulsion was detected in one patient due to ifosfamide. Osteopenia developed in 14 of the 380 patients (3%) who took steroids, with three of these patients experiencing an altered gait. A convulsion developed after cytosine arabinoside in one patient (0.5%) of the 178 patients who received intrathecal cytosine arabinoside.

Table 6. Neurological complications and mortality

	Number of patients who died (n=101) (%)	Number of living patients (n=480) (%)	Total (N=581)*	p
With neurological complications	51 (50.4)	176 (36.6)	227 (39.1)	0.010
Without neurological complications	50 (49.5)	304 (63.3)	354 (60.9)	

*: There were 581 patients for whom survival information was available.

Survival information was available for 581 patients. Neurological complications were more common in patients who died (p=0.010) (Table 6).

DISCUSSION

In a study on adult cancer, it was shown that at least one neurological complication develops in 15% of patients with cancer. Similar to the study in pediatric patients, this rate ranges from 12.5% to 54.4%.[3] The rate of neurological complications for all tumors at our center is 39%.

In various studies, the rate of neurological complications in patients with ALL has been reported to range from 3% to 18.4%.[4,5] In this study, the rate was found to be 47%. At the time of diagnosis, pathology was detected in the neurological examination, central involvement was observed in cranial imaging, or the presence of suspicious findings in the cytological and/or biochemical examination of the cerebrospinal fluid (CSF) sample taken by lumbar puncture was evaluated as indicative of central nervous system (CNS) involvement. Patients with CNS involvement at initial diagnosis were included in this study. Leukemic involvement of the CNS, side effects related to treatment, and cerebrovascular events were considered. Conversely, other studies excluded patients with CNS involvement at diagnosis. The high rate of neurological complications in our study has been linked to this inclusion criteria.

Neurological complications in lymphomas are attributed to direct infiltration of the CNS, compression, ischemia, paraneoplastic syndromes, and immune deficiency induced by malignancy and treatment complications. In the literature, the rate of neurological complications across all lymphomas has been reported at 8.9%. Neurological complications have been more frequently reported in NHL; their frequency varies between 12.2% and 31.8%.[6,7] This may be attributed to the fact that NHL is more common in childhood, the rate of extranodal involvement is higher in NHL, and the course of NHL is more aggressive than that of HL.[8] In this study, the rate of neurological complications in NHL was found to be 30%, consistent with the literature.

The diagnosis of CNS tumors was delayed by several months in some patients due to non-specific findings. Headache is the most common symptom, with a prevalence of 32.2% to 71% reported in studies.[9] In this study, we demonstrated a headache rate of 48.3% in patients with CNS tumors. Similar to these studies, impaired balance, weakness, seizures, visual disturbances, abnormal eye movements, and facial paralysis were identified as the most common symptoms.

While headaches are common in childhood, underlying serious illnesses are rare. In our study, the most frequent complaints in patients with brain tumors before diagnosis were headaches, nausea, and vomiting, yet 19% of the patients did not have any complaints other than headaches. A child presenting with a headache could be misdiagnosed with a migraine rather than a CNS tumor. Therefore, cranial imaging is recommended for patients presenting with headaches accompanied by vomiting and neurological findings.[10]

Headaches may occur due to a decrease in intracranial pressure following a lumbar puncture (LP). Complications from lumbar puncture, such cerebrospinal fluid leak, can lead to low-pressure headaches. One study reported an 8% incidence of headache following LP, a rate that increases to 50% among adolescents. In our study, LP-related headaches were detected in six patients (1.7%). This low rate may be attributable to unrecorded events. Treatments such as intravenous caffeine, hydration, and blood patches may be useful. Using a smaller bore needle with minimal trauma may also prevent headaches. Additionally, pseudotumor cerebri, which can result in headaches, may be caused by retinoids, steroids, and electrolyte abnormalities.[2]

Seizures are less common in adults than in children with neoplastic diseases (5.4%), likely due to the immaturity of children's brains. Factors increasing the risk of seizures include gray matter involvement, supratentorial location, ganglioglioma, dysembryoplastic neuroepithelial tumor, and oligodendroglioma. Seizures may also result from leukemic infiltration of the brain, brain metastases from solid tumors, and brain injuries secondary to chemotherapy or radiotherapy. Metabolic and morphological changes, including malformations of cortical development, underlie the pathophysiology of seizures. A study by Antunes et al.[11] found the seizure rate to be 7% across all solid tumors and hematological malignancies. In our study, convulsions were observed in 7.8% of all cases. Approximately 40 years ago, the

causes of seizures could not be identified in more than 70% of patients due to limitations in neuroradiological techniques. In the past 20 years, the underlying causes of seizures have been identified in 83–85% of patients. In the present study, we identified underlying causes in 80.3% of cases.

Seizures continue in a small proportion of cancer patients. In our study, seizures were not prolonged, and none progressed into chronic epilepsy. There were no deaths attributed to seizures. Antiepileptics should not be used long-term in the absence of an underlying neurological deficit. In one study, the frequency of patients using anticonvulsants for more than one year is 35%.[12] In our study, 54.8% of the patients used antiepileptic for over a year, with an average usage of 16.6 months.

Posterior reversible encephalopathy syndrome (PRES) is a clinical diagnosis characterized by headache, mental deterioration, visual changes, hypertension, and changes observed in brain magnetic resonance imaging (MRI). The administration of chemotherapeutic agents both intrathecally and intravenously, as well as hematopoietic stem cell transplantation, increases the risk of PRES. The frequency of PRES varies between 1.8% and 3.9% in patients with ALL.[4] The rate of posterior reversible encephalopathy syndrome due to methotrexate ranges from 5.4% to 37% in patients with ALL.[13] Posterior reversible encephalopathy syndrome was not observed with any drug except intrathecal methotrexate. Seizures were noted in all patients with PRES, and one of them, a patient with chronic myeloid leukemia, had high blood pressure. The susceptibility to PRES is especially increased by ALL induction therapy, bone marrow transplant (BMT), and the use of immunosuppressive agents.[14] No patients who underwent BMT developed PRES, but it occurred frequently during ALL induction therapy. Treatment involves cessation of the offending drug, administration of anti-seizure medication, reduction of blood pressure, and monitoring for seizures. Dextromethorphan has been used in some patients to decrease methotrexate neurotoxicity. Neurological deficits may not be reversible.[15]

Although many studies have shown PRES to be the most common complication, in the present study, peripheral neuropathy due to vincristine was the most common complication associated with ALL (18.5%).

Chemotherapy-induced peripheral neuropathy (CIPN) is a potentially long-lasting adverse effect of commonly used chemotherapy agents in pediatric practice, notably vincristine and other vinca alkaloids, cisplatin, and carboplatin.[16] The treatment or prevention of peripheral neuropathy is not well-defined. Symptoms may regress after cessation or dose reduction of vincristine. Complete improvement has been observed with the combination of pyridoxine (150 mg/m^2/day in two oral doses) and pyridostigmine (3 mg/kg/day in two oral doses) administered for three weeks.[4,17] In this study, it was observed that 94% of the patients received at least one treatment (pyridoxine and pyridostigmine); these treatments were well-tolerated and resulted in no side effects.

Visual complaints, such as decreased visual acuity, double vision, and eye movement disorders, may occur. They are most commonly associated with drugs such as opioids, steroids, and antiseizure medications. Visual dysfunction was not detected in our patients with ALL. In this study, CNS tumors, metastases, and cerebrovascular events were the most common causes of visual dysfunction.[18]

Cisplatin, carboplatin, and cranial external beam radiation therapy may be associated with acute hearing loss. In our study, hearing loss was mostly attributed to cisplatin (4.3%). Vitamin E may offer some protection.[19]

A study found that among half of all cancer patients who showed improvement, 30% of those who developed neurological complications died.[5] This study demonstrated that the risk of mortality increases across all cases when compared to those without neurological complications.

Limitations of the Study

Given that this is a retrospective study, it is possible that the data may be insufficient.

CONCLUSION

It is important to consider all aspects of patient care when evaluating neurological complaints. As previously explained, children with cancer often present many predisposing factors for neurological symptoms. Compared to adults, pediatric cancer patients are particularly sensitive to both cancer and its treatment. Neurological complications not only affect the quality of life but are also associated with increased mortality among cancer patients. It is critical to recognize that such complications can arise at the time of diagnosis, during treatment, or after treatment has concluded.

As anticipated, neurological complications are most frequently observed in patients with brain tumors. In children with systemic cancer, undergoing chemotherapy and RT heightens the risk of neurological complications. Such complications contribute to increased patient mortality. Therefore, it is crucial to strike a balance between treatment efficacy and the management of complications.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 24.07.2015, number: 2015-327).

Author Contributions: Concept – EU, HP; Design – EU, HP, LK; Supervision – SK, HG; Resource – MK, MAO, TP, MC; Materials – AO, EY; Data Collection and/or Processing – EU, HP, LK; Analysis and/or Interpretation – EU, HP, LK, FE; Literature Search – EU, HP; Writing – EU, HP, LK; Critical Reviews – EU, HP, HG.

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