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Neurotoxicity as a major problem in childhood hematology

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ABSTRACT

The study examined the frequency of neurological complications in children with acute leukemia caused by chemotherapy. Among the patients, the majority had neurological manifestations related to the treatment. The most common complication was vincristine-induced polyneuropathy. Leukencephalopathy associated with methotrexate was also frequently observed, manifesting as seizures and stroke-like symptoms. These complications most often occurred at certain stages of treatment, which underscores the need for careful monitoring and adjustment of therapy to minimize negative outcomes.

INTRODUCTION

Thanks to the latest advances in anti-leukemia drugs and supportive treatment methods, as well as risk-based therapeutic approaches, LCO chemotherapy protocols have now been developed and are being used, providing the patient with a recovery probability of 80-90% in ALL and 60-70% in OML [1,2]. This led to a shift in emphasis from strengthening treatment to achieving cure with fewer side effects. Progress has been achieved through the use of minimal residual disease (MMR) monitoring to adjust treatment intensity according to clinical response, and more recently through the introduction of targeted immunotherapy.

Complications related to treatment are among the causes of deaths in children with onco-hematological pathology and can cause a violation of the protocol, withdrawal or reduction of the dose of drugs. Violations in the treatment protocol, in turn, can reduce the effectiveness of the treatment and increase the frequency of relapses of the underlying disease [4,7]. Complications related to treatment are classified as «early acute complications» when they develop in the first 2 weeks of treatment, as «complications during therapy», when they develop after 2 weeks of treatment and as «late complications», when they develop after recovery from the last dose of chemotherapy. The time of onset of neurotoxic complications, their diversity and degree of expression are individual for each patient [3,5].

In this article we decided to describe the clinical and neurological characteristics of patients with neurological complications due to polychemotherapy. Neurological symptoms and signs associated with chemotherapy were observed in 151 out of 238 children, which represented 63.4% of the total number of patients grouped by syndromic features. The average age of children in the group was - 7 6 (3;10) years (Me; (Q1; Q3)).

Side-effects of chemicals were classified according to the Common Terminology Criteria for Adverse Events (version 3).

We studied the main clinical syndromes that occur in children during polychemotherapy. One of the most common neurological complications after chemotherapy was polyneuropathy in 58 (38.4%) cases, which was 38.4% and corresponds to foreign literature. Further, 31 patients (20.5%) had acute hheadache on the applied drug; in this case, children with LOP had APRO and headaches started after 30 minutes of use of this drug; the headaches were high, pulsating character and not bought by analgesics.

Acute methotrexate neurotoxicity confirmed by MRI of the brain with contrast was observed in 23 cases (15.2%). One of the common symptoms of methotrexate neurotoxicity were convulsions, stroke-like episode of motor disorders, reduced vision and motor disorders.

Posterior reversible encephalopathy syndrome (PRES) were observed in 4 girls with ALL, at the induction phase and characterized by visual disorders: double vision, cortical blindness, hemianopia, as well as focal convulsions, comorbidity, headache and elevated blood pressure.

The mechanism of development of PRES in patients, especially in children with acute leucosis remains unexplored. One of the main pathophysiological hypotheses for the development of PRES in children with acute leukaemia is a violation of the blood-brain barrier due to a sudden increase in arterial pressure. There is also membrane instability and increased permeability of the Blood-brain barrier as a result of electrolyte disturbances, which in turn can lead to PRES. On magnetic resonance imaging (MRI) the weighted T2 and FLAIR sequences show vasogenic edema, which mainly affects the white matter of the back of the temporal and posterior parts of the brain [3, 12].

The authors of the article Noje C, Cohen K, Jordan LC (2013) pointed to the acute stroke both hemorrhagic and ischemic in patients after the application of L- Asparagine, which has the property of causing deficiency of antithrombin, plasminogen, fibrinogen and factors IX and XI. L-asparagine is used in induction therapy for children with ALL and is related to the initial state of hypocoagulation, followed by a suspected hypercoagulation condition that can lead to thrombosis. L-asparginite-associated

thrombotic strokes typically occur at the end of induction, usually 7-10 days after induction is complete, and may lead to convulsions, a focal neurological deficit or, less frequently, a coma. In our work, acute stroke accounted for 3.3% of all cases in the second group.

Chemical meningitis as one of the most common chemotherapy complications in our study was found at the induction stage in 2 (1.3%) children.

Infectious lesions of the nervous system were observed in 8 cases (5.3%), encephalitis in 3 cases, in 1 case toxoplasmosis encephalitis, fungal brain damage, acute transverse myelitis and in 2-In the cases of patients developed acute demyelinating polyradiculoneuritis Landry, which unfortunately ended in death.

Table 1. Final diagnosis in children in 2 group by age

When studying neurological complications due to chemotherapy by age, the data showed the following.

Diagnosis	Over 10 years	Under 10	Total
Hemorrhagic acute stroke	0 (0,0%)	3 (2,0%)	3 (2,0%)
Ischemic acute stroke	0 (0,0%)	2 (1,3%)	2 (1,3%)
Peripheral Polyneuropathy	19 (12,6%)	37 (24,5%)	56 (37,1%)
Encephalopathy after COVID	2 (1,3%)	1 (0,7%)	3 (2,0%)
Neurasthenia	9 (6,0%)	22 (14,6%)	31 (20,5%)
Leukoencephalopathy (MTX)	1 (0,7%)	22 (14,6%)	23 (15,2%)
PRES Syndrome	4 (2,6%)	0 (0,0%)	4 (2,6%)
Landy syndrome	2 (1,3%)	0 (0,0%)	2 (1,3%)
Acute myelitis	0 (0,0%)	1 (0,7%)	1 (0,7%)
Convulsive syndrome	4 (2,6%)	10 (6,6%)	14 (9,3%)
Toxoplasmosis encephalitis	0 (0,0%)	1 (0,7%)	1 (0,7%)
Fungal defeat of CNS	1 (0,7%)	0 (0,0%)	1 (0,7%)
Meningitis	0 (0,0%)	2 (1,3%)	2 (1,3%)
Cerebral syndrome	0 (0,0%)	1 (0,7%)	1 (0,7%)
Epileptic encephalopathy	0 (0,0%)	5 (3,3%)	5 (3,3%)
Secondary tumor	0 (0,0%)	1 (0,7%)	1 (0,7%)
Relapse without the neurol. symptoms	0 (0,0%)	1 (0,7%)	1 (0,7%)
Total	**42 (27,8%)**	**109 (72,2%)**	**151 (100,0%)**

Хи-квадрат - 34,35, p-value – 0,005

Chemoinduced polyneuropathy was observed more frequently in children under 10 years of age in 24.5% of cases and was more often characterized by the disappearance of the Achilles, further patellar reflexes, as well as the presence of sensitivity disorders. Methotrexaty leukoencephalopathy was found in children younger than 10 years, which is most likely characterized by immaturity of the nervous system (myelination deficiency). Unlike other nosocomial diseases, PRES occurred only in children over 10 years of age and was characterized by visual impairment that quickly recovered within 3-4 days. Convulsive syndrome and epilepsy were observed more often in children younger than 10 years.

Selin Aytaç, Sevgi Yetgin, Betül Tavilon have done a lot of work to investigate the neurotoxicity of children's chemotherapy in Turkey. Out of 260 patients, 40 had neurotoxicity. The majority of neurological symptoms - 82.5% were observed at all stages of therapy, while in the rest of cases at the later stages of therapy, which also corresponds to our research results [1,12].

Table 2. Acute and sub-acute neurotoxicity at different stages of therapy

	Induction	Consolidation 1	Consolidation 2	Console 3	Supportive therapy	Total
MTH-Leyko	2 (8,0%)	10 (40,0%)	3 (12,0%)	6 (24,0%)	4 (16,0%)	23 (16,6%)
Peripheral Polyneuropathy	22 (42, 3%)	7 (13,5%)	8 (15,4%)	10 (19,2%)	5 (9,6%)	52 (34,4%)
Acute Ischemic stroke						

Acute hemorrhagic stroke	2 (1,3%) 2 (66,7%)				 1 (33,7%)	2 (1,3%) 3 (2,0%)
PRES	4 (100%)					4 (2,6%)
Convulsions/epilepsy/epilepticus encephalopathy	4 (30,8) 1 (33,3%) 1 (50%)	1 (7,7%) - -	3 (23,1%) - -	1 (7,7%) 1 (33,3%) -	4 (30,8%) 1 (25%) 1 (50%)	13 (8,6%) 3 (2%) 2 (1,3%)
Acute headache	18 (60,0%)	5(16,7%)	5 (16,7%)	1 (3,3%)	1 (3,3%)	30(20,5%)
Myopathy	5 (100%)					5 (3,3%)
Infection: Fungal defeat of CNS Landry acute myelitis Covid encephalitis Toxoplasma encephalitis	 1 (100%) 1 (50%) 2 (75%) 1 (100%)	 1 (100%)		 1 (25%)	 1 (50%)	 1 (0,7%) 2 (1,3%) 1 (0,7%) 3 (2,0%) 1 (0,7%)
Meningitis (chemical)	2 (100%)					2 (1,3%)
Acute cerebral ataxia	1 (100%)					1 (0,7%)
Secondary tumor	1 (100%)					1 (0,7%)
Total	70 (46,4%)	24 (15,9%)	19 (12,6%)	20 (13,2%)	18 (11,9%)	151 (100%)

Seizures were one of the main manifestations of neurotoxicity and occurred in 13 patients (8.6%) cases out of all cases in 2 group. Focal convulsions occurred in 80% of cases, which does confirm the fact of specific infiltration of CNS. Seizures were reliably higher (30.8%) in children at the induction and supportive therapy stage. In some cases, seizures (7%) were a manifestation of a transient ischemic attack, which was also a manifestation of neurotoxicity.

In 35% of cases, the first sign of methotrexate leukoencephalopathy. In 75% of cases, neurotoxicity was demonstrated at an early stage (induction of remission).

Methotrexate leukoencephalopathy was found in 23 cases, which amounted to 16.6%. These changes were more reliably observed at consolidation stages 1 and 3. Neurological symptoms and signs appeared between 2-9 (average 7.5 days) days after receiving methotrexate and disappeared after 2-6 days (average 4.5 days). The symptoms of MTHX-leukoencephalopathy were varied and could be either intensified or reduced.

The main signs of toxic leukaemia were convulsions in 30.4%, facial nerve neuropathy in 4.3% of cases, which was characterized by nuclear damage, which was evidenced by the alternation syndrome of Miyar Gubler syndrome. Transient stroke-like syndrome in 21.7%, visual impairment in 4.3% and headaches in 13% of cases.

One of the frequently occurring complications with a variety of clinical-neurological symptoms was methotrexate leukoencephalopathy, which in each case was confirmed by neuroimaging. The interesting fact was that the clinical picture resembled a transient ischemic attack, but differed in a longer course (from 1 day to 5 days). Convulsions were one of the most frequent manifestations of methotrexate leukoencephalopathy and were more often characterized by complex focal attacks.

Four patients with MTX neurotoxicity were observed at each stage of chemotherapy and focal attacks were observed for 1 or 2 days of MTX administration, regardless of the use of anti-epileptic drugs. Brain MRI showed an increase in white matter focal points with each treatment step. In 5% of children with methotrexate leukoencephalopathy, leukaemia was detected only by routine brain MRI, these patients did not complain and during the examination they did not detect focal neurological disorders.

According to Birol Baytan MD, Melike Sezgin Evim MD cerebrovascular manifestations were found in 5/23 children; 21.7%, where thrombosis was observed in 4 cases and intracranial hemorrhage in 1 - m case [57; C.312-318]. The above changes were observed due to the use of L- Asparagine, given that this drug causes a disturbance in the pro-and anticoagulant system. In our study, cerebral venous sinus thrombosis was reported in 2 cases and these cases were associated with the use of L-Asparagine. In both patients the onset of the disease was convulsions (100%), headache (100%) and focal neurological deficit. The children were 4, 5 and 9 years old. Venous sinus thrombosis was observed by us only at the stage of induction of remission, which is characterized by an initial specific infiltration of the brain by the vascular cells in these patients.

When we studied the general neurotoxicity by treatment stages, it can be seen that statistically more often neurological complications were observed at the induction stage in 46.4% of cases, which included dexamethasone (), vinkristin (1.5 mg/ m2), daunorubicin (30 mg/ m2), L-Asparagine (5,000 U/m2), citarabine (75 mg/m2), cyclophosphamide (1 g/m2) and 5 times the intrathecal application of the methotrexate according to age. In the remaining treatment stages, no reliable difference was observed, so on consolidation 1 - 15.9%, consolidation 2 - 12.6%, consolidation 3 - 13.2% of cases in the whole group where children received a high dose of methotrexate and took 6-mercaptopurin as well as daunorubicin (30 mg/m2), L-Asparaginaze (2500 U/m2), citarabin (75 mg/m2), dexamethasone, ethoposide, vinkristin and three intrthecal therapies (methotrexate, prednisolone and citarabine depending on age). In the last supporting phase, which lasts 74 weeks - neurological complications accounted for 11.9% of cases. At the support stage, convulsive states and methotrexate leukoencephalopathy were often observed.

Of all the neurotoxicity cases, death was 10.8%, corresponding to 16 patients out of 151. Improvement and partial regression of neurological manifestations in children after treatment were noted in 82 children, which was 55.4%. 37 children (25%) successfully passed the next stage of therapy and started treatment.

Outcome after treatment	Over 10 years	Under 10	Total	Chi-square	p-value
Unchanged	4 (2,7%)	8 (5,4%)	12 (8,1%)	4,426	0,351
With improvement	24 (16,2%)	58 (39,2%)	82 (55,4%)		
Worsening	1 (0,7%)	0 (0,0%)	1 (0,7%)		
Moved to the next stage	7 (4,7%)	30 (20,3%)	37 (25,0%)		
Fatal outcome	5 (3,4%)	11 (7,4%)	16 (10,8%)		
Total	**41 (27,7%)**	**107 (72,3%)**	**148 (100,0%)**		

Table 4. Outcome of children in the group by age.

The number of patients with a good neurological status who moved on to the next stage of treatment was 80%.

75% of the deaths occurred in a group of children under 10 years old, which suggests that children at this age are more vulnerable. The main percentage of 37.5% was progression of the main disease, infection and sepsis were 43.8%. ONMC, renal failure in 1 case was detected in a group of children younger than 10 years without any reliable difference (Chi-Square = 8, p = 0.156). Although sepsis was found in a group of young children.

Table 5. Causes of mortality in children in the group by age

Cause of death	Over 10 years	Under 10	Total	Chi-square	p-value
Progression of major disease	1 (6,3%)	5 (31,3%)	6 (37,5%)	8	0,156
Vinkristin side effect	1 (6,3%)	0 (0,0%)	1 (6,3%)		
Infection	2 (12,5%)	1 (6,3%)	3 (18,8%)		
Stroke	0 (0,0%)	1 (6,3%)	1 (6,3%)		
Sepsis	0 (0,0%)	4 (25,0%)	4 (25,0%)		
Renal failure	0 (0,0%)	1 (6,3%)	1 (6,3%)		
Total	**4 (25,0%)**	**12 (75,0%)**	**16 (100,0%)**		

CONCLUSION

Neurotoxicity (secondary complications) as one of the serious neurological complications prevailed over the number of primary complications (related to the main disease) in a ratio of 3:1. The main acute manifestation of neurotoxicity (final diagnosis of 2 groups) was chemo-induced polyneuropathy in 38.4%, MTHX leukemia in 15.2% of cases, steroid myopathy 35%, convulsive syndrome in 8.6% of cases, hemoglobin, Cerebral sinus thrombosis in 3.3%, SSOE in 2.6% of cases in the second group of patients. Major acute and low neurotoxic syndromes in 46.4% of cases were observed at the induction stage, in 15.9% at consolidation stage 1, in 13.2% at consolidation stage 3 and at supportive therapy stage in 11.9% of cases, confirming the fact that the most vulnerable period is induction stage, as patients arrive initially in a severe and sometimes critical condition and against this background begins chemotherapy. Lethality was more prevalent in children under 10 years of age, and the cause of death was the progression of the main disease, sepsis, HCM, renal failure and the side effect of vinkristin.

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