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CENTRAL NERVOUS SYSTEM INVOLVEMENT IN NON-HODGKIN'S LYMPHOMA*

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Lymphomas are the third most common malignant neoplasms of childhood. It is the second most prevalent malignant neoplasm after leukemias encountered in our experience[1,2]. In the past decade advances in histopathology, immunology and cytogenetics have resulted in better understanding of the biology of non-Hodgkin's lymphoma (NHL). In recent years, the application of intensive combined modality approaches, featuring multiple drugs, radiation therapy and prophylactic treatment of the central nervous system (CNS) showed dramatic improvement in treatment results of childhood NHL[2-7].

In this study we evaluated CNS involvement in 458 NHL cases that were treated in the Pediatric Oncology Unit of Hacettepe University Children's Hospital.

Material and Methods

Four hundred and fifty-eight children with NHL (Burkitt's lymphoma excluded) were followed in the Pediatric Oncology Unit of Hacettepe University Children's Hospital between January 1972 and December 1983. The patients who showed CNS involvement at the time of diagnosis and in the follow-up period were included in this study. The cases were studied retrospectively with regard to age, sex, localization and extent of tumor, histopathologic subgroups and therapeutic results.

The disease was histologically classified according to the Rappaport classification[3]. The patients were staged clinically according to the Murphy classification for childhood NHL[4].

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CNS involvement was determined by clinical evaluation, cerebrospinal fluid examinations and neuroradiologic findings.

Results

Twelve patients (2.6%) showed CNS involvement at the time of diagnosis, five of which had bone-marrow infiltration, and three bone-marrow involvement during the follow-up period.

The ages of this group ranged between 2.5 - 14 years with a mean age of 7.1. Forty-one and a half percent of these children were in the 5-9 year-old age-group and 41.5 percent were in the 10-14 year-old age-group. The male/female ratio was 2/1.

Table I lists the primary tumor sites in our patients. Abdominal localization of tumor, the most common site in our study group, accounted for two hundred and sixty-three of our patients (57.4%). CNS disease was most frequently observed in the patients who presented with peripheral nodal primary (4.4%).

Distribution of patients with CNS involvement according to histopathologic diagnosis is shown in Table II. Forty-two percent of the patients were diagnosed cytologically. Twenty-five percent of the patients were characterized as poorly differentiated lymphocytic lymphoma. Since four patients came from other hospitals, our pathologists were unable to specify their histopathologic subgroup.

Only six patients with CNS involvement at the time of diagnosis showed complications (Table III). In three cases, the most common complication was hyperuricemia.

Four of the 12 patients with CNS involvement did not respond to therapy, and two patients died at the beginning of therapy. The remainding six patients were treated with the protocol seen in Table IV. Only two patients achieved complete remission.

Four hundred and forty-six patients were free of CNS involvement at the time of diagnosis. Thirty-two of them (7.1%) showed CNS infiltration during the follow-up period, and nine of these patients also showed bone-marrow involvement with CNS relapse. Their ages ranged from 2.5-14 years with a mean age of 6.4 years. Forty and a half percent were in the 5-9 year-old age-group. The male/female ratio was 5.4.

All of 32 patients were classified as Stage III at the time of diagnosis according to the Murphy staging system.

The principal tumor sites in 32 patients who showed CNS involvement in the follow-up period are seen in Table V. No significant difference was observed between peripheral nodal, mediastinal and abdominal localization for CNS

involvement. However, six patients with abdominal tumors also had mediastinal involvement.

Thirty-seven percent of the 32 cases in our study group were histopathologically classified as poorly differentiated lymphocytic lymphoma according to the Rappaport classification system. The other subgroups are seen in Table VI.

The onset of CNS involvement was 18.7 ± 2.0 weeks from the initial diagnosis and this was significantly shorter than the bone-marrow involvement, which was found to be 35.6 ± 5.8 weeks in our other study[5] ($p<0.01$). The time of CNS involvement in the follow-up period is shown in Table VII. In 16 percent of the patients CNS involvement occurred in the first two months.

Nine of 32 patients received CNS prophylactic therapy. Seventeen of the remainding 23 patients were diagnosed and followed before 1978, however chemotherapy protocols of that period did not contain CNS prophylactic therapy. The other six patients were not given prophylactic therapy because of socioeconomic reasons and prolonged induction therapy with concomitant infection. The onset of CNS involvement was 18.7 ± 2 weeks in 32 patients who

TABLE I: Localization of Primary Tumor and CNS Involvement at Time of Diagnosis

Localization of Tumor	CNS Non-involved No. of cases		CNS involved No. of cases		Total No. of cases
Peripheral nodal	43	(95.6%)	2	(4.4%)	45
Mediasten	68	(97.2%)	2	(2.8%)	70
Abdomen	257	(97.8%)	6	(2.2%)	263
Disseminated	53	(96.4%)	2	(3.6%)	55
Other	25	(100 %)	–	–	25
Total	446	(97.4%)	12	(2.6%)	458

TABLE II: Histopathologic Subgroups of 12 NHL Patients with CNS Involvement at Time of Diagnosis

Histopathologic Subgroup	No. of cases	
Poorly differentiated lymphocytic	3	(25%)
Unclassified	4	(33%)
Cytologic diagnosis	5	(42%)
Total	12	(100%)

showed CNS involvement in the follow-up period. This period was 25.2 ± 3.2 weeks in the group of nine cases who received CNS prophylaxis and 16.1 ± 2.3 weeks in the group of 17 patients who did not. The difference between the two groups was significant ($p<0.01$).

The CNS relapses were systematic in two of the nine patients who received CNS prophylactic therapy. In seven patients the relapses were confined to only the CNS.

TABLE III: Complications Observed in Six NHL Patients with CNS Involvement at Time of Diagnosis

Complication	No. of cases	
Hyperuricemia	3	(50%)
V. Cava Superior Syndrome	1	(17%)
Gastrointestinal Obstruction	2	(33%)
Total	6	(100%)

TABLE IV: Therapeutic Outcomes of Six NHL Patients with CNS Involvement at Time of Diagnosis

Resistant: two cases

1. Oncovin Prednisolone
   - Craniospinal X-ray (3000 r Cr, 2400 r Sp)
   - Intrathecal MTX (12 mg/M^2)
2. COP
   - Intrathecal MTX (12 mg/M^2)

Complete remission: two cases

1. COP
   - Craniospinal X-ray (3000 r Cr, 2400 r Sp)
2. A-COP
   - Cranial X-ray (3000 r) – Triple Intrathecal Therapy (Mtx 12 mg/M^2, Prednisolone 30 mg/M^2, Ara-C 30 mg/M^2)

Partial remission: two cases

1. COP
   - Craniospinal X-ray (3000 r Cr, 2400 r Sp)
2. A-COP
   - Cranial X-ray (3000 r) – Intrathecal MTX (12 mg/M^2)

Cr: Cranial, Sp: Spinal, COP: Cyclophosphamide, Oncovin, Prednisolone.
A-COP: Adriamycin, Cyclophosphamide, Oncovin, Prednisolone, MTX: Methotrexate.

TABLE V: Localization of Primary Tumor and CNS Involvement in the Follow-up Period

Localization of Tumor	CNS Non-involved No. of cases		CNS involved No. of cases		Total No. of cases
Peripheral nodal	40	(93.1%)	3	(6.9%)	43
Mediasten	62	(91.2%)	6	(8.8%)	68
Abdomen	235	(91.5%)	22	(8.5%)	257
Disseminated	52	(98.2%)	1	(1.8%)	53
Other	25	(100 %)	–	–	25
Total	414	(92.9%)	32	(7.1%)	446

TABLE VI: Histopathologic Subgroups of 32 NHL Patients Demonstrating CNS Involvement in the Follow-up Period

Histopathologic Subgroup	No. of cases	
Poorly differentiated lymphocytic	12	(37%)
Lymphohistiocytic	1	(3%)
Undifferentiated	6	(19%)
Unclassified	8	(25%)
Cytological Diagnosis	5	(16%)
Total	32	(100%)

TABLE VII: Time Interval between Diagnosis and CNS Involvement in 32 NHL Patients

Time of CNS Involvement (mo.)	No. of cases	
0 - 2	5	(16%)
3 - 6	21	(65%)
7 - 12	5	(16%)
13 - 24	1	(3%)
Total	32	(100%)

TABLE VIII: Treatment Protocols and Prognosis of 19 Patients Who Did Not Receive CNS Prophylactic Therapy

Treatment Protocols	Exitus during therapy	Resistant	Remission	Total
I.T. Methotrexate	–	2	1	3
Craniospinal X-ray	–	2	1	3
Craniospinal X-ray and IT MTX	2	4	2	8
Cranial X-ray and IT MTX	–	3	–	3
Cranial X-ray and triple IT	–	–	1	1
Triple IT (MTX, ARA-C, Predn.)	–	–	1	1
Total	2 (10.5%)	11 (58%)	6 (31.5%)	19 (1%)

IT: Intrathecal, MTX: Methotrexate, Ara-C: Cytosine Arabinoside, Predn: Prednisolone

TABLE IX: Life Span of 28 Patients Who Died after CNS Relapse

Life Span After Relapse (mo.)	No. of Cases	
0 - 2	16	(57.0%)
3 - 6	8	(28.5%)
7 - 12	3	(11.0%)
13 - 24	1	(3.5%)
Total	28	(100%)

Two of the nine patients who received CNS prophylactic therapy could not be followed after the CNS relapses. Of the remaining seven, one patient died of disease during induction therapy, three patients were resistant to the therapy and three patients attained remission (42.8%). However, later, one patient in the latter group died of a recurring CNS relapse three months after the first CNS involvement, the second patient could not be followed after one year when he showed systemic CNS and bone marrow relapse, and the third patient is still in remission 11 months following initial diagnosis.

Four of the 23 patients who did not receive CNS prophylactic therapy discontinued the therapy administered after the first relapse. The chemotherapy protocols given to the remaining 19 patients are shown in Table VIII. No comparison between the various protocols was made because of the limited number of cases.

In six of the patients, remission could be reattained, however three of these patients died of systemic relapses after remission had been induced. The surviving three have been under control for 10 years, 3.5 years, and 7 months.

The mean survival time, in the 28 patients, who showed CNS involvement in the follow-up period and died was 13.1 ± 3.3 weeks after the first relapse. Their life spans after the first relapses are shown in Table IX. Fifty-seven percent of the cases died in the first two months and 28.5 percent died in 3-6 months.

As a result, four out of 32 patients who showed CNS involvement in the follow-up period are still alive. One of 9 patients who received CNS prophylactic therapy is alive and in complete remission 11 months after initial diagnosis. Three out of 23 patients who did not receive prophylactic therapy are alive. The first case has been in complete remission for ten years, the second has been in complete remission for seven months, and the third is alive after 3.5 months with a primary tumor in complete and a CNS tumor in partial remission.

Discussion

Considerable progress has been made during the past decade in the treatment of childhood non-Hodgkin's lymphoma. With the advent of successful systemic therapy, primary relapse in the central nervous system emerged as an important obstacle to cure[6-9].

CNS involvement at the time of diagnosis in children with NHL is unusual. In most series, it is reported to be between O and 6 percent. The overall involvement of the CNS occurs in about 30 percent of children with NHL. In patients with primary mediastinal or bone-marrow involvement, the risk approaches 50 percent[2,7]. The incidence of CNS involvement at the time of diagnosis was 2.6 percent in our series. The overall incidence was 9.7 percent (at the time of diagnosis and in the follow-up period). This low incidence rate of CNS involvement can be explained by the fact that abdominal localization of the primary tumor in our patients was twice as great when compared with the literature[2,6-9].

CNS prophylaxis has been successful in reducing the risk of CNS involvement[2,6-12]. In our study, we also demonstrated that the onset of CNS involvement was shorter in patients who did not receive CNS prophylaxis than in those that did. However, we observed that CNS involvement occurred in 16 percent of our cases before the initiation of CNS prophylaxis with the Modified-COP and Adriamycin-COP chemotherapy protocols. For this reason, CNS prophylactic therapy must be given earlier to patients who are at high risk of CNS involvement. In recent years, early CNS prophylaxis for children with NHL has been accomplished by combination therapy consisting of cranial irradiation and intrathecal chemotherapy or only intrathecal chemotherapy[9-15]. With the <SA2 - <2 protocol, CNS

involvement has been reduced to 17 percent[2,10]. Good results have been reported with other modern combined chemotherapy protocols[11-15]. In our study, the incidence of CNS involvement was already low (9.7%), but to further reduce this we started to administer CNS prophylactic intrathecal chemotherapy early to patients with mediastinal and non-resectable abdominal primary tumors. We also decided to add craniospinal irradiation after remission in patients with mediastinal involvement. In addition to systemic and intrathecal chemotherapy, two monthly intravenous and intrathecal therapy treatments were programmed as a pulse in the maintenance period. The results of these studies will be published in the near future.

Summary

From January 1972 to December 1983, we studied central nervous system (CNS) involvement in 458 patients with non-Hodgkin's lymphoma at Hacettepe University Children's Hospital. All the cases were studied retrospectively with regard to age, sex, localization and extent of tumor, histopathologic subgroup and therapeutic results and were compared with other series. CNS disease was present in 12 patients (2.6%) at the time of diagnosis and 32 children (7.1%) demonstrated CNS involvement in the follow-up period. The onset of CNS involvement was 25.2 ± 3.2 weeks in patients who had received CNS prophylactic therapy and 16.1 ± 2.3 weeks in patients who did not. Modifications in the chemotherapy protocols and more aggressive combined chemotherapy protocols are discussed.

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