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CENTRAL NERVOUS SYSTEM COMPLICATIONS IN ACUTE LEUKEMIA OF CHILDHOOD

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Burns first recognized and reported a case of leukemia with neurological involvement in 1923.[1] Since then many reports have appeared in the literature.[2-14] It is stated that the incidence of central nervous system (CNS) involvement in acute leukemia has increased since the use of modern chemotherapy which produces long-lasting remissions and prolonged survival. CNS complications may develop in relapse and in remission; patients even come in with CNS symptoms and later are diagnosed as having leukemia.[13] Sometimes a patient without positive clinical symptoms or findings was found to have CNS infiltration at autopsy.[10, 14]

The most common CNS complications of the acute leukemias are: a) intracranial hemorrhage, b) infiltration of the meninges and brain by leukemic cells and c) infection. Hemorrhage, which is generally subarachnoidal or subdural, is the most frequent complication. Thrombocytopenia and leukocytosis [15] (over 300,000/cmm) are the main etiological factors. Leukemic infiltration is generally into the meninges and less frequently into the brain substance. Infections are usually the end result of decreased resistance caused by antileukemic drugs and altered immunological mechanisms during the course of the disease.

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Symptoms and findings in meningeal leukemia are those produced by increased intracranial pressure, such as headache, lethargy, convulsions, nausea, vomiting, stiff neck and papilledema. In some cases infiltration causing pressure on the cranial nerves may initiate palsies of the related nerves along with less specific neurological signs.[7, 8, 10, 11, 16]

In children, generally, cranial sutures are separated. The pressure of cerebrospinal fluid (CSF) is increased and pleocytosis is present. Often the CSF sugar is decreased and protein content is increased. Cultures yield no growth.

In this paper we will present our experience with CNS involvement in children with acute leukemia seen in this hospital from January 1958 to March 1967.

Material

Our material consists of 200 children, aged 3.5 months to 16 years, who were diagnosed as acute leukemia in the Hematology Clinics of Hacettepe Children's Hospital. Fifty of these were lost to follow-up. Twenty-six of the remaining 150 children had central nervous system complications, two being asymptomatic and discovered at postmortem examination. Only ten of the 20 patients autopsied presented positive pathology.

The diagnosis of leukemia was made by a positive bone marrow. Lumbar punctures were done on patients with signs of CNS involvement. Pressure, cell count, examination of the smear, determination of sugar and protein, and cultures were carried out.

Until 1964, prednisolone (1 - 2 mg/kg/day), 6 M.P. (2.5 mg/kg/day) and methotrexate (1.25, 2.5 or 5 mg/day) were given in combinations. After that, cyclic therapy[19] with the addition of cyclophosphamide (2 - 5 mg/kg/day) was used. Supportive therapy was also instituted as needed. Meningeal involvement was treated either by intrathecal methotrexate (0.3 - 0.5 mg/kg) or radiation (400 - 600r) to the skull.

Pathological evaluations of the CNS complications were done by reviewing autopsy reports and routine sections from the brain.

Results

Twenty-four out of 150 patients presented symptoms and signs of central nervous system involvement. Eight of these were also

examined by autopsy. In addition, two asymptomatic patients were discovered to have CNS involvement at autopsy, bringing the total number of cases whose CNS involvement was confirmed by autopsy to ten. The incidence of CNS involvement in our series was 17.3 per cent. There were 26 episodes related to CNS involvement in 24 patients.

There were 20 males and six female patients whose ages ranged from three years to 16 years, with a mean age of 8.7 years. The types of leukemia were as follows : 20 acute lymphoblastic, three acute myelogenous and three acute stem cell (undifferentiated).

Five patients were in remission and 19 were in relapse when the neurologic complications first developed. Six patients were admitted to the hospital with signs of increased intracranial pressure and were later diagnosed as having acute leukemia. The symptoms and signs of the CNS involvement are summarized in Table 1. The hematological findings on the 24 patients are tabulated in Table 2.

CSF pressure was found to be increased (over 200 mm H_2O) in each case. The protein content of the CSF varied between 25 and 248 mg/100 ml and was higher than 40 mg/100 ml in all but one patient. Sugar ranged from 32 mg to 255 mg/100 ml. The

TABLE 1

THE FREQUENCY OF THE SYMPTOMS AND SIGNS OF CNS INVOLVEMENT

	Number of Patients	Percentage
Papilledema	14	58.3
Vomiting	13	54.1
Nuchal Rigidity	10	41.6
Headache	10	41.6
Cranial Nerve Palsies	9	37.9
(7th nerve palsy	5)	
(6th nerve palsy	3)	
(6th and 7th nerve palsy	1)	
Separation of Sutures	8*	33.3
Convulsions	3	12.5

* Only 21 patients had skull x-rays.

TABLE 2

SUMMARY OF THE HEMATOLOGICAL FINDINGS AT THE TIME OF CNS INVOLVEMENT

	Number of Cases	Percent
Hemoglobin (gm/100 ml) < 5	10	41.6
5 - 10	6	25.0
> 10	8	33.3
WBC (per cmm) < 5000	7	29.1
5000 - 10,000	3	12.5
10,000 - 25,000	8	33.3
25,000 - 100,000	3	12.5
> 100,000	3*	12.5
Thrombocytopenia	21	87.5
Blasts in peripheral smear	11	45.8
Blasts in the bone marrow	19**	79.1

* The WBC of these three were 128,000, 131,000. 240,000 respectively.

** Five patients were in remission at the time of CNS involvement and had no blasts in the bone marrow.

cell count was 0 to 600 per cmm and consisted mainly of mononuclear cells and blasts.

The interval between the diagnosis of leukemia and the CNS involvement varied from one day to 25 months, with a mean of 7.58 months. In ten patients, CNS complications developed during the first five months after the diagnosis of leukemia was made. This period was 5.7, 7, 8, 10.5, 12, 13, 19 and 25 months in eight additional cases: In six patients CNS symptoms were the presenting signs. The duration of life after these complications developed was from one day to 12 months, with a mean of 2.52 months. Thirteen patients died within the first month of development of the complications. Five died within 1.5 to four months and three 7.5, 11.5 and 12 months after the CNS involvement. The mean survival in this series of 21 patients was 8.8 months, ranging from four days to 29 months. Three patients are alive at the time of this report for 2.5 months, four months and 16 months after the diagnosis of this complication.

The therapy given was radiation to the skull in four and intrathecal methotrexate (varying from one to four injections) in twelve cases. Eight patients did not have any specific therapy related to their CNS symptoms other than corticosteroids.

Autopsy findings of the ten patients are tabulated in Table 3. In one case the meningeal infiltration was grossly diagnosed as meningitis. Later microscopy showed diffuse meningeal leukemic infiltration. In ancther patient perivascular infiltration was limited to the choroid plexus. Figures 1 and 2 show the pathological findings in our cases.

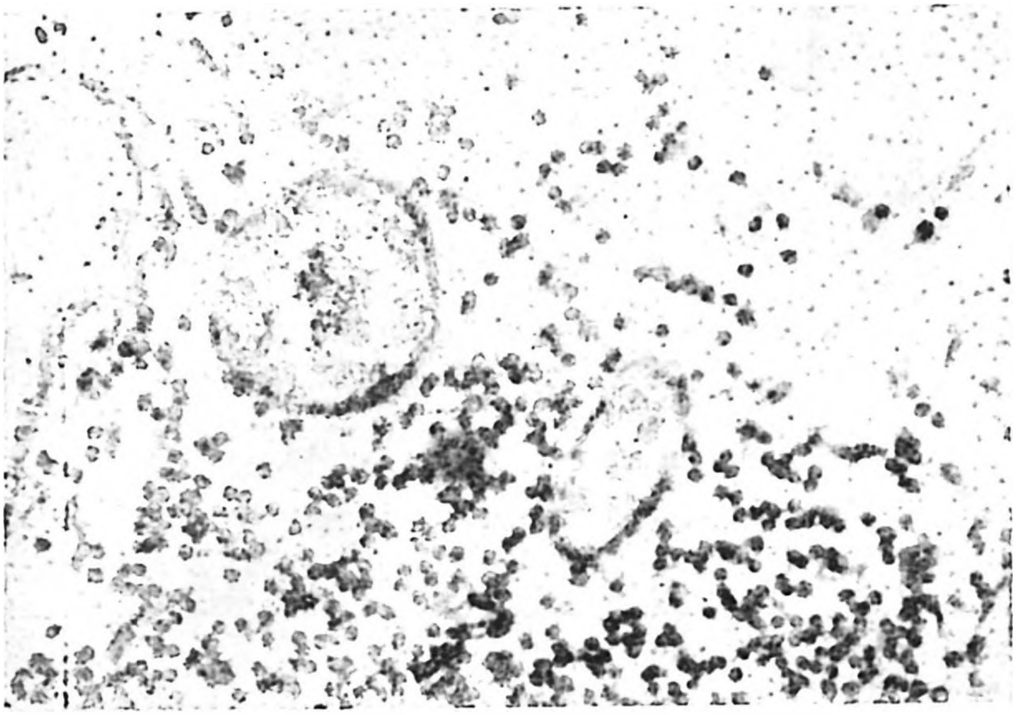

Figure 1. Meningeal leukemic infiltration.

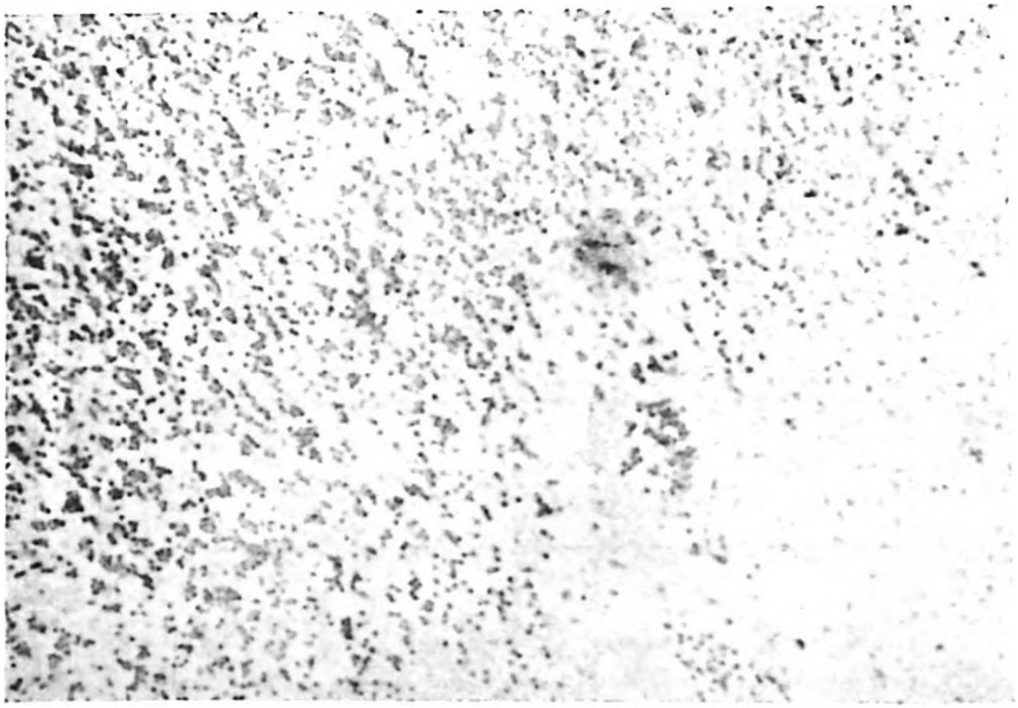

Figure 2. Leukemic infiltration into brain substance.

TABLE 3
AUTOPSY FINDINGS

Age	Sex	Type of Leukemia	Leukemic infiltrations				Hemorrhages			Clinical signs or symptoms present
			Meninges		Brain*		Subdural	Sub-arachnoid	Intra-cerebral	
			Perivascular	Diffuse	Perivascular	Other**				
9	F	ALL	—	—	—	+	+	—	—	yes
3.5	M	Stem cell	+	+	—	+	—	+	+	yes
6	M	ALL	+	+	+	—	—	—	—	yes
13	F	AML	—	+	+	—	—	—	—	yes
4	M	ALL	—	+	—	—	—	—	—	yes
7	M	ALL	—	—	+	—	—	—	—	yes
3.5	F	ALL	—	—	+	—	—	—	—	yes
3	F	Stem cell	—	—	+	—	—	—	+	yes
4	F	ALL	—	—	+	+	—	—	+	no
8	M	ALL	+	+	+	+	—	+	+	no

* Cerebrum, cerebellum and pons.
** Leukemic infiltrations around hemorrhagic areas and foci in the brain substance.

Discussion

It is generally believed that the incidence of CNS involvement in acute leukemia is increased after obtaining long remissions by the use of modern chemotherapy.[11, 14, 17] The incidence of CNS involvement in acute leukemia in children varies from 3.4 per cent to 52.4 per cent in different series (Table 4). The incidence in our series was 17.3 per cent which is slightly lower than recent reports. It is claimed that patients who expire during the first three months of the disease generally will not have this complication. Since 38 of the 150 patients in our series expired within three months of diagnosis, this may well explain our somewhat lower incidence. The male : female ratio in our cases with CNS involvement was 3.3 : 1. This was 2.6 : 1 in the total 200 patients. Although some authors found a preponderance of males,[3, 17] some claim no significant sex difference in patients with CNS involvement.[8, 10, 14, 18]

TABLE 4

INCIDENCE OF CNS INVOLVEMENT IN DIFFERENT SERIES

Author	Year	Percent	Number of Patients	Survival After Onset of CNS Involvement (months) Mean	Median
Wells and Silver[8]	1957	52.4	(42)		
Leidler and Russell[3]	1945	35.0			
Diamond[20]	1934	28.5			
Bass[21]	1921	26.0			
Sullivan[7]	1957	25.0*			
Pierce[11]	1962	19.3	(232)	7.3	
Norlander[22]	1951	17.5	(154)		
Steffey[10]	1961	16.2*			
Moore at al[9]	1960	13.6			
		3.4*			
D'Angio[23]	1959	10.5	(372)		
Kirshbaum and Preuss[24]	1943	10.0	(123)		
Brandt[25]	1945	8.6	(205)		
Lightwood et al[26]	1960	4.0	(100)		
Schwab and Weiss[2]	1935	22.5*	(120)		
Shaw et al[17]	1960	16.7*	(150)	3	9.7
Evans et al[30]	1964	28.0	(480)		
Hyman et al[14]	1965	26.0	(132)		3.5
Haghbin and Zuelzer[18]	1965	29.8	(205)	4.9	4.0

* Only meningeal involvement included.

The majority of our patients was affected by acute lymphoblastic leukemias, which agrees with the reported series.[14, 18] About one-fourth were in remission at the time of neurologic involvement. Pierce,[11] Hyman et al,[14] Shaw et al [17] and Haghbin and Zuelzer [18] reported similar results in their patients with CNS involvement stating that in some series up to 50 per cent were in remission at the onset of CNS infiltration. The failure of the antileukemic agents (except corticosterioids) to cross the «blood-brain barrier» in effective concentration might be responsible for the development of CNS infiltrations. It is conceivable that the leukemic cells persisting in the meninges lead to eventual hematological relapse. We observed no particular tendency for the complications of the central nervous system to develop during the administration of any one particular antimetabolite : 11 patients were on 6 M.P., four on methotrexate and two on cyclophosphamide. The frequency of the signs of increased intracranial pressure in our patients is consistent with other authors' reports.[3, 14, 17, 18]

The symptoms were relieved after lumbar puncture in most of the patients and the findings began to disappear at the end of the first week or so of methotrexate or radiation therapy.

We did not observe hyperphagia or behavior disturbances such as those which were first reported by Sansone [4] and later by others,[7, 14, 17] in association with CNS involvement in leukemic children, but six patients had pathologic weight gain before the development of symptoms.

Recent studies have suggested that intracranial hemorrhage due to thrombocytopenia is predominantly into the subarachnoidal area, but the hemorrhage frequently extends into the brain substance and sometimes nodules of leukemic cells may be seen in the areas of hemorrhage.[9] Our autopsy findings (Table 3) were similar to those of other authors; however, none of our cases showed evidence of infection at postmortem examination.

The hematological findings did not have any relation to the signs and symptoms except for thrombocytopenia which was present in 87.5 per cent of the cases.

Separation of the sutures of the skull was noted in the skull roentgenograms of one-third of our patients. It develops mainly because of increased CSF pressure, but some authors claim that leukemic infiltration of the suture lines is responsible for this separa-

tion.[27] Shaw et al[17] did not find such infiltration at the suture lines in their patient who was examined microscopically.

The cerebrospinal fluid findings of our patients were in accord with the previous reports.[11, 14, 17, 18] The decreased sugar level of the CSF may be due to either increased glycolysis by the leukemic cells [2, 28] or to alterations in the «blood-brain barrier» which causes a decrease in the diffusion of glucose across this membrane.[29] In our patients we found no correlation between increased cell count and high CSF pressure. The suggestive role of the high CSF cell count in early recurrence of this complication could not be evaluated because of the limited number of patients with repeated episodes.

In regard to the type of therapy of the CNS infiltration, lumbar puncture alone may alleviate the signs of increased intracranial pressure,[30] but in addition intrathecal methotrexate is used widely in many centers with good response. Intrathecal methotrexate was administered to six patients in one dose, to four patients in two doses, and to two patients in four doses at intervals varying from three to five days. No side effects related to the drug were observed in these twelve patients. Radiation therapy was given to four patients and repeated in one case for a relapse which occurred 2.5 months after the initial CNS infiltration. Again, other than temporary epilation, no side effect was observed following radiation to the skull. Since the number of cases treated by the two different methods were small, we cannot draw any conclusions as to the preferred type of therapy. We do not, however, give prophylactic intrathecal methotrexate to our patients as suggested by some authors.[30] Radiation is spared for the cases who become refractory to methotrexate therapy or for deeply localized lesions. Corticosteroids may also reach cerebrospinal fluid and resolve some of the leptomeningeal infiltration and may provide some neurological improvement.[17]

Prognosis is said to be grave after CNS symptoms have developed in leukemic children, [11, 17] but others claim the opposite.[18] In our 24 patients with meningeal involvement, the mean and median survivals were 8.8 and 7.5 months respectively. The mean and median durations of life after the onset of CNS involvement were 2.52 months and 0.6 months, which is shorter than the latest reported series [11, 14, 17, 18] (Table 4). Haghbin and Zuelzer [18] claim that following 42 months of survival, no CNS infiltration develops; however, this view needs to be confirmed. The time between the onset of the disease and the first CNS involvement was 7.58 months (mean) and

5 months (median). Analysis of our cases also suggests that the prognosis in acute leukemia is poor after central nervous system involvement.

Summary

Central nervous system complications in 150 children with acute leukemia were analysed and an incidence of 17.3 per cent was found. Symptomatology, clinical and laboratory findings, therapy and prognosis are reviewed and compared with the published reports in the literature.

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