Central Nervous System Involvement by Leukemia in Children. I. Relationship to Systemic Leukemia and Description of Clinical and Laboratory Manifestations

By CAROL B. HYMAN, JAMES M. BOGLE, CHARLES A. BRUBAKER, KENNETH WILLIAMS AND DENMAN HAMMOND

Present understanding of the pathologic and clinical implications of central nervous system (CNS) infiltration by leukemia is based on reports involving relatively small numbers of patients. Some previous reports have dealt with neurologic complications of all types in association with leukemia including hemorrhage and infection as well as involvement of the CNS by leukemia.

This report deals exclusively with CNS involvement by the leukemic process. No distinction is made between involvement of the brain, meninges or nerve roots. The data is based on observations of 109 episodes due to CNS infiltration which occurred in 59 children with leukemia. A clinical description of CNS leukemia including incidence in relation to systemic leukemia, effect on the prognosis for duration of life and signs, symptoms and laboratory findings is presented. A separate communication reports the experience in management of CNS leukemia with intrathecal methotrexate.

Clinical Material

All 59 children with leukemia who developed CNS involvement were diagnosed and managed for their entire course of illness at the Children's Hospital of Los Angeles, Division of Hematology. There were 37 males and 22 females. The age range was from 14 months to 14 years with a median age of 5½ years. The types of leukemia included acute undifferentiated and lymphocytic (55), acute and subacute granulocytic (2), monocytic (1) leukemia and subacute erythroleukemia (1). No instance of CNS involvement with chronic granulocytic leukemia was observed.

Methods

The patients were seen at regular intervals by members of the Division of Hematology.
Table 1.—Signs and Symptoms of CNS Involvement Occurring in 59 Patients

<table>
<thead>
<tr>
<th>Secondary to Increased CSF Pressure (56 Pts.)</th>
<th>Psychic Disturbances (12 Pts.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>Hyperirritability 8</td>
</tr>
<tr>
<td>Headache</td>
<td>Hallucinations 3</td>
</tr>
<tr>
<td>Papilledema</td>
<td>Catatonic depression 1</td>
</tr>
<tr>
<td>Lethargy</td>
<td>Disorientation 1</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Cushing's Syndrome (8 Pts.)</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>Pathologic weight gain 8</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Hirautism 1</td>
</tr>
<tr>
<td>Coma</td>
<td>Auditory Disturbances (5 Pts.)</td>
</tr>
<tr>
<td>Proptosis</td>
<td>Hypoacusis 4</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Hyperacusis 2</td>
</tr>
<tr>
<td>Ocular Disturbances (21 Pts.)</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>Diplopia</td>
<td>Dysfunction (6 Pts.)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>Hyperpnea 3</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Cheyne-Stokes respiration 2</td>
</tr>
<tr>
<td>Blindness</td>
<td>Fever 1</td>
</tr>
<tr>
<td>Photophobia</td>
<td>Hiccough 1</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Tachycardia 1</td>
</tr>
<tr>
<td>Other visual disturbances</td>
<td>Speech Disturbances (3 Pts.)</td>
</tr>
<tr>
<td>Cranial &amp; Peripheral Nerve Dysfunction (13 Pts.)</td>
<td>Dx. by CSF 2</td>
</tr>
<tr>
<td>Facial paralysis</td>
<td>Asymptomatic Episodes (3 Pts.)</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>Dx. at autopsy 1</td>
</tr>
<tr>
<td>Paraplegia</td>
<td></td>
</tr>
<tr>
<td>Foot drop</td>
<td></td>
</tr>
<tr>
<td>Ptoasis eyelid</td>
<td></td>
</tr>
</tbody>
</table>

At each visit records were made of symptoms, physical findings, blood and bone marrow examinations. Bone marrow aspirations were done every four to six weeks regardless of the patient's apparent disease status. The four categories: symptoms, physical findings, blood and bone marrow were evaluated according to the criteria adopted by Acute Leukemia Cooperative Chemotherapy Study Group A. Whenever CNS involvement was suspected, a lumbar puncture was performed and the cerebrospinal fluid (CSF) examined.

**C**linical and **L**aboratory **M**anifestations of **CNS** **L**eukemia

**General Information and Method of Analysis**

Diagnosis of CNS leukemia was based on a synthesis of all available information including signs, symptoms and laboratory findings. Recurrent episodes in the same patient were separated by a disappearance of abnormal signs, symptoms and/or laboratory findings, usually in response to specific therapy directed against the CNS disease.

The 59 patients with CNS involvement experienced 109 separate episodes. Thirty-four patients had only one episode of CNS involvement, twelve patients had two, six patients four, two patients five, and one patient had seven separate episodes.
Signs and Symptoms

Abnormal CNS signs, symptoms or both were observed in 107 of the 109 episodes. The frequency of each manifestation listed in table 1 is related to the number of patients in whom it occurred rather than to the number of episodes in which it occurred. The possibility of the occurrence of a specific sign or symptom in a given patient is of particular interest while the total number of times it recurs is less meaningful.

The signs and symptoms which directed attention to the CNS were, in order of decreasing frequency, manifestations of increased CSF pressure, ocular disturbances, cranial and peripheral nerve dysfunction, psychic disturbances, Cushing's syndrome, auditory disturbances, various evidences of autonomic nervous system dysfunction, and speech disturbances.

Fifty-six of the 59 patients developed signs or symptoms of increased CSF pressure. The most common were vomiting, headache, papilledema and lethargy. There were two patients who did not develop signs or symptoms of increased CSF pressure yet had increased CSF pressure when lumbar puncture was performed for other neurologic indications. The third asymptomatic patient did not have a lumbar puncture; CNS involvement was detected at autopsy.

Ocular disturbances were next in frequency occurring in 21 patients. Most common were diplopia, strabismus and blurred vision; however, three patients developed blindness.

Cranial and peripheral nerve dysfunction other than those causing ocular disturbances occurred in 13 patients. Facial paralysis was most frequent but paraplegia and hemiparesis also occurred.

Psychic disturbances manifested by extreme hyperirritability, hallucinations, catatonic depression and disorientation occurred in 12 patients.

Cushing's syndrome, manifested by pathologic weight gain, hirsutism and acne, occurred in eight patients and was not associated with steroid therapy.

Auditory disturbances, autonomic nervous system dysfunction and speech disturbances were observed less frequently. Of these, hyperpnea, Cheyne-Stokes respiration and slurred speech led to the diagnosis of CNS involvement in several instances.

Laboratory Findings

Cerebrospinal Fluid: Observations of CSF pressure, white cell count, sugar and protein obtained from the initial lumbar puncture for each episode are summarized in table 2.

The CSF was examined at the onset of 101 episodes. One or more abnormalities were noted in 95 of these, whereas in six there were no abnormal findings. These latter cases of apparent CNS leukemic involvement with no abnormalities in CSF findings are to be discussed more fully.

The most consistent abnormality, increased CSF pressure, occurred in 91 per cent. The total white cell count in the CSF was almost as frequently
affected, being increased in 84 per cent. CSF sugar was below normal in 55 per cent, within the normal range in 35 per cent and above normal in 10 per cent. CSF protein determinations were of little value in diagnosing CNS leukemia. Values were within the normal range in 76 per cent of the observations, above normal in 21 per cent and below normal in 3 per cent.

The median values for CSF findings given in table 2 compare closely to mean values for CSF findings observed by Evans in patients with symptoms of meningeal involvement. Characteristically, in patients with CNS leukemia, the initial CSF pressure is increased, white cell count increased, protein normal and sugar decreased.

In 64 instances, the CSF was cultured for bacteria. All cultures were negative. Bacterial meningitis in a child with leukemia has not been observed in this clinic, although other types of infections including septicemia are not uncommon.

Electroencephalogram: Electroencephalograms performed on 36 of the patients were interpreted as normal in eight and abnormal in 27. There was no consistent abnormality. In 20 of the 27, there were diffuse dysrhythmias; eight of these had slowing of the cycles. In the remaining seven, only a portion of the brain appeared to be affected; the changes included sporadic increased voltage, slowing of the cycles, and disorganization in the bifrontal area.

Skull X-Ray: X-rays of the skull were performed in 37 patients. Eighteen of these were normal and 19 had evidence of increased intracranial pressure. One patient showed, in addition, demineralization and erosion of the floor of the sella turcica.

Post-Mortem Findings

At the time of this analysis, one of the 59 children under study is still alive, one is lost to follow-up and 57 have died. Post-mortem examination of the central nervous system was performed on 43.

The post-mortem findings were categorized according to the presence or absence of central nervous system involvement with leukemia. Leukemic in-
volvement was considered to be present whether it was meningeal, localized, or diffuse throughout the brain. If hemorrhage alone was found, the classification was "no involvement." Of the 43 patients on whom post-mortem CNS examinations were performed, 32 showed CNS involvement and 11 did not.

**Evidence for CNS Involvement in Six Patients with Normal CSF Findings**

There were six patients in whom the CSF findings were normal, yet the patients had CNS involvement by leukemia. In five, lumbar punctures were performed because of marked symptomatology referable to the CNS. In the sixth case, it was done as part of a baseline study before administering a potentially neurotoxic drug. The latter patient also had an abnormal electroencephalogram showing diffuse slowing. Death occurred three weeks after the CSF examination and at autopsy there was infiltration of the meninges by leukemia.

In one case, the diagnosis of CNS leukemia was made, despite normal CSF findings, on the basis of hyperirritability, hydrocephalus with proptosis, and widening of the sutures of the skull on x-ray. These findings improved after skull irradiation. Hydrocephalus recurred three months later, and at autopsy, after another three months, there was massive involvement of the brain and meninges by leukemia.

Three symptomatic patients died six weeks to three months after normal CSF examination. In each of these, the diagnosis of CNS involvement was confirmed at autopsy.

Autopsy findings did not confirm the clinical diagnosis of CNS involvement in one patient who died 11 days after a negative CSF examination. This patient had papilledema, diplopia, and hallucinations noted by several observers. Therapy included radiation to the skull and intravenous hydrocortisone after which the papilledema and CNS symptoms completely disappeared. It is known that steroids can reduce meningeal inflammatory reactions\(^\text{13}\) and that CNS leukemia frequently responds to steroids.\(^\text{1,2}\) It is also known that radiation is effective in the treatment of CNS leukemic involvement\(^\text{1,2,4,14}\) and clinical improvement may occur within the first few days of therapy. It seems reasonable to assume that in this patient the CNS infiltration was sufficiently sensitive to combined steroid-radiation therapy to disappear completely within the 11 days prior to death.

One additional patient, not included in the six patients described above, was observed to have a decreased CSF sugar but otherwise normal CSF findings. This patient had a facial paralysis and two months later, at autopsy, CNS involvement was confirmed.

**Relationship of Central Nervous System Involvement to Systemic Leukemia**

**Incidence**

The percentage of children with leukemia who develop CNS involvement is uncertain and appears to have increased with the longer life span incident to therapy.\(^\text{1,3}\) Other factors which also influence the apparent incidence in-
inclusion: criteria for diagnosis, whether based on exclusively clinical or pathologic findings or both, and the awareness of the observer.

In order to obtain data on the incidence of CNS involvement, the course of 132 children with leukemia observed from diagnosis to death, except for four who are alive at this time, was analyzed. The patients were diagnosed in the years 1957, 1958 and 1959, during which time all children were observed carefully for CNS disease. Thirty-four (26 per cent) developed CNS involvement.

Analysis of the sex distribution of the 132 children shows that CNS involvement occurred in 15 of the 49 females (32 per cent) and 19 of the 83 males (23 per cent). Females with leukemia developed CNS involvement with slightly greater frequency than males. In contrast, Shaw in reviewing reported cases including both adults and children found meningeal leukemia almost twice as frequently in males. In his experience in children he reported one female and 20 males with the complication. Moore described meningeal leukemia in 20 children with CNS involvement and found equal sex distribution. Our findings and those of Wells indicate that there is probably no significant difference in the sex incidence. There is no reason to suspect that the occurrence of CNS leukemia would be sex related.

Interval from Diagnosis of Leukemia to Onset of CNS Involvement by the Disease

The interval from the diagnosis of leukemia to recognition of CNS involvement in 132 patients, 34 of whom developed CNS disease, is illustrated in figure 1. The number of patients still living at intervals after diagnosis is also shown as well as the incidence of CNS involvement in the surviving patients.

CNS symptomatology led to the original diagnosis of leukemia in three patients. CNS involvement developed uncommonly during the first three months of the disease. However, after this period there was a sharp increase in incidence so that half of the cases of CNS involvement were recognized by seven months after diagnosis. CNS involvement occurred at all times throughout the course of disease from pre-diagnosis to as late as four years thereafter.

Status of Systemic Disease at Onset of CNS Episodes

It is well known that CNS manifestations of leukemia can occur while the systemic disease is apparently under good clinical control. The leukemia status of 59 patients at the onset of each episode of CNS involvement was analyzed using the criteria of the Acute Leukemia Cooperative Chemotherapy Study Group (table 3). In 32 episodes, the systemic disease was considered to be in complete remission (Status I, No Apparent Disease). Twenty-eight of these showed signs or symptoms of CNS involvement; the remaining four were asymptomatic. Three of the four were diagnosed by lumbar puncture and one by autopsy. At the onset of 25 CNS episodes, there was only minimal clinical evidence of leukemia (Status II, Mild Disease). At the onset of 34 CNS episodes, the systemic leukemia was in
Fig. 1.—Time to onset and incidence of CNS involvement in 132 children with leukemia. The height of each column shows the number of patients living at the beginning of each of the stated intervals after diagnosis. Comparison of the number of patients with newly diagnosed CNS leukemia (in black) plus those patients with previously diagnosed CNS leukemia (cross-hatched) to the total height of the column shows the proportion of patients with and without CNS involvement at various intervals after diagnosis.

Leukemia Therapy and the Development of CNS Involvement

There was no apparent relationship between the antileukemia therapy that had been employed and the development of CNS involvement (table 5). The number of patients who had been treated with each of the various agents was much the same as the frequency with which these agents were prescribed.

Review of the therapy given immediately prior to or at the time of diagnosis of initial CNS involvement revealed that 18 patients were receiving antipurines, 29 were receiving a folic acid antagonist and six were receiving steroids.

Forty-seven of the 59 patients had their first clinical manifestation of CNS disease while receiving an antimetabolite. This may be explained by the inability of 6-mercaptopurine and methotrexate, in standard oral dosages, to cross the blood-brain barrier in sufficient concentration to prevent the development of CNS leukemia.2,15,16

More of our patients received antipurines than methotrexate prior to the onset of CNS involvement, yet fewer were on antipurines than on methotrexate at the time their symptoms developed. This is perhaps due to the order of the treatment schedule employed. Most patients received antipurines...
Table 3.—Status of Systemic Leukemia at Onset of 109 CNS Episodes in 59 Patients

<table>
<thead>
<tr>
<th>Status of Systemic Leukemia*</th>
<th>No. Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. No apparent disease</td>
<td>32</td>
</tr>
<tr>
<td>II. Mild disease</td>
<td>25</td>
</tr>
<tr>
<td>III. Moderate disease</td>
<td>34</td>
</tr>
<tr>
<td>IV. Advanced disease</td>
<td>18</td>
</tr>
</tbody>
</table>

*See Reference 10.

Table 4.—Bone Marrow Findings at Onset of 109 CNS Episodes in 59 Patients

<table>
<thead>
<tr>
<th>Marrow Rating*</th>
<th>No. Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No evidence of leukemia</td>
<td>58</td>
</tr>
<tr>
<td>2. Moderate leukemic involvement</td>
<td>9</td>
</tr>
<tr>
<td>3. Marked leukemic involvement</td>
<td>42</td>
</tr>
</tbody>
</table>

*See Reference 10.

Table 5.—Leukemia Therapy and the Development of CNS Involvement

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Therapy Prior to Onset</td>
<td>Therapy at Onset</td>
</tr>
<tr>
<td>Purine antagonists</td>
<td></td>
</tr>
<tr>
<td>(6-mercaptopurine, thio-</td>
<td>53</td>
</tr>
<tr>
<td>guanosine)</td>
<td>18</td>
</tr>
<tr>
<td>Folic acid antagonists</td>
<td></td>
</tr>
<tr>
<td>(methotrexate)</td>
<td>40</td>
</tr>
<tr>
<td>Steroids (prednisone)</td>
<td>39</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>None</td>
<td>4</td>
</tr>
</tbody>
</table>

as initial therapy followed by prednisone and later by methotrexate. The mean duration of response to 6-mercaptopurine is only 4.1 months while the median interval from the onset of leukemia to the onset of CNS involvement in this group was approximately seven months. Therefore, many of the patients were refractory to 6-mercaptopurine and were on other therapy by the time CNS involvement developed.

The relative paucity of patients who developed CNS involvement while on prednisone therapy substantiates the impression that the steroid hormones in standard oral dosage are effective to some extent in controlling CNS symptomatology. We have observed improvement in CNS symptoms when systemic therapy was changed from an antimetabolite to prednisone.

Influence of CNS Involvement on Prognosis for Survival

The 132 children diagnosed as having leukemia in the years 1957 through 1959 and whose entire course to date has been observed, survived from zero days to 58 months, median 9.4 months. The 34 patients in this group who developed CNS involvement had a survival time of zero days to 42 months, median 10.6 months, whereas that of the 98 patients without CNS involve-
CNS INVOLVEMENT BY LEUKEMIA IN CHILDREN 1

Fig. 2.—Comparison of survival with and without CNS involvement of children with leukemia. This shows survival of 132 children with leukemia diagnosed during the years 1957, 1958 and 1959. Thirty-four developed CNS involvement and 98 did not. Note the sharp decline in the survival curve during the first three months in patients who did not, as compared with the group who did develop CNS involvement. The median survival time of 320 days in patients with CNS involvement is compared with 259 days in patients without CNS involvement.

The onset of CNS involvement does not imply that the systemic disease is in a terminal phase. Figure 3 shows the duration of survival of 59 patients after the time of onset of CNS involvement.

Although one patient expired on the day CNS involvement was diagnosed, the median survival time after CNS disease was recognized was 3½ months. Eight patients (14 per cent) lived one to three plus years thereafter.

Our data and that of Sosa18 is at variance with those of Shaw2 and Pierce4 in that survival time was apparently not shortened in patients with CNS disease.

SUMMARY AND CONCLUSIONS

Observations on the course of 59 children who experienced 109 distinct episodes of CNS involvement by leukemia showed that:

1. This complication may be associated with all types of acute and subacute leukemia.

2. There is no single or combination of diagnostic criteria. Manifestations
of increased CSF pressure, such as vomiting, headache, and papilledema are the most frequent clinical findings. However, it should be emphasized that CNS involvement may be associated with normal CSF findings.

3. CNS involvement may be present at the onset of leukemia or can occur at any time during the course.

4. Approximately 26 per cent of children with leukemia develop CNS involvement.

5. CNS involvement may occur when the disease is under apparently good therapeutic control as well as during relapse.

6. There is no relationship between the agents which had been previously used to treat the systemic disease and the later development of CNS involvement. However, the onset of CNS symptoms was less frequent when the systemic disease was under treatment with steroids.

7. The development of CNS involvement does not appear to shorten the survival time of patients with leukemia when treatment for CNS involvement is given.

**Summario in Interlingua**

Cinquanta-novem juveniles esseva observate in 109 distincte episodios de affection del systema nervose central attribuibile a leucemia como factor causative. Es formulate le sequente constatationes:

1. Affection del systema nervose central pote occurrer como complication de omne typos de leucemia acute e subacute.

2. Il non existe un specific criterio diagnostic. Etiam, il non existe un combination de criterios diagnostic. Manifestaciones de un augmento del pression in le liquido encephalo-rhachidian—i.e. vomito, mal de capite, e papilledema—es le constatationes clinic le plus frequente. Tamen, il debe esser notate que
CNS INVOLVEMENT BY LEUKEMIA IN CHILDREN

affection del sistema nervioso central pote esser associate con normal constata- tiones del liquido encephalo-rachidian.

3. Affection del sistema nervioso central pote esser presente al momento del declaration de leucemia o pote occurrer a non importa qual tempore in le curso de illo.

4. Approximativemente 26 pro cento del juveniles con leucemia disveloppa un affection del sistema nervioso central.

5. Affection del sistema nervoso central pote occurrer quando la leucemia es apparentemente ben stabilisate o etiam quando la patiente es in recidiva.

6. Il existe nulle relation inter le previemente usate agente therapeutic contra le morbo constitutional e le subsequente disveloppamento de affection del sistema nervoso central. Tamen, la declaration de symptomas del sistema nervoso central esseva minus frequente quando le leucemia esseva sub tractamento con steroide.

7. Le disveloppamento de affection del sistema nervoso central non pare reducir le longevitate del patiente con leucemia, providite que le affection del sistema nervoso central es tractate appropriatemente.

ACKNOWLEDGMENTS

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