NEUROLOGIC COMPLICATIONS OF LEUKEMIAS
AND LYMPHOMAS*

WILLIAM E. HUNT, M.D., BERTHA A. BOURONCLE, M.D.,
AND JOHN N. MEAGHER, M.D.

Division of Neurosurgery, Department of Surgery, and Department
of Medicine, Ohio State University, Columbus, Ohio

(Received for publication October 10, 1957)

Since the first report of complications of the nervous system in leukemia by Burns in 1823, there have been sporadic case reports in the medical literature. Schwab and Weiss, in a review of the literature from 1835 to 1935, found 146 cases of leukemia with neurologic complications. They also reported a case of their own in which the patient had headache, nausea and vomiting, and multiple cranial-nerve involvement which responded temporarily to roentgen-ray treatment.

In 1927, Trömmer and Wohlwill reported 12 cases of leukemia, with neurologic complications in 9 of these. At necropsy in 11 of the 12 cases (91 per cent) there was microscopic evidence of invasion of the central nervous system.

Critchley and Greenfield in 1930 reported a series of patients with chloroma and leukemia who exhibited spinal symptoms. Another 14 cases of leukemia with cerebral involvement were added by Diamond. Five of these were myelogenous, 4 lymphatic, 2 myeloblastic, 2 stem cell, and one monocytic in type. In all cases he described infiltration of the pia mater and perivascular spaces. He stated that the infiltration about the chiasm could give rise to papilledema.

In 1945 Leidler and Russell reported 20 cases of their own and reviewed a total of 65 cases of leukemia with neurologic complications. They concluded that 80 per cent of patients with leukemia have significant pathologic changes in the brain and that 20 to 35 per cent of patients with leukemia have neurologic symptoms and signs. In their series, hemorrhage into the central nervous system was the cause of death in 29 per cent of cases.

Sparling et al. in 1947 reported neurologic complications in 20 per cent of lymphatic leukemias in their series and alluded to infiltration of arachnoidal membranes and perineurium of cranial nerves in patients with signs of meningeal irritation, cranial-nerve palsies, headache and diplopia. They noted transient improvement in such patients when treated with small doses of roentgen rays to the cranial vault, and commented that the pathogenesis of the infiltrate was not well understood since the neurologic complications could occur when peripheral blood was normal.

* Presented in part to the Society of Neurological Surgeons, St. Louis, Missouri, May 17, 1957.
Sansone\textsuperscript{12} in 1954 reported 2 cases of children with acute lymphatic leukemia in whom, during remission of the disorder in peripheral blood and bone marrow, there developed headache, visual defects, meningeal symptoms, paresthesias, and papilledema. There was increase in cerebrospinal fluid pressure, white cells, and protein, with decreased sugar and negative cultures. Separation of the sutures and convolutional atrophy were present on roentgenograms of the skull. These patients showed transient improvement when treated with intrathecal Aminopterin, but later blindness developed, and they died of their disease.

In a more recent article Wells and Silver\textsuperscript{18} (1957) reported the neurologic manifestations of a group of 63 patients with acute leukemias.

As regards involvement of the central nervous system in Hodgkin’s disease, syndromes produced by spinal and cranial involvement have been described.\textsuperscript{10} Fifty-four such cases were recorded in the literature up to 1929; in 42 of these the lesions were spinal extradural and 12 were cranial lesions. Goldman and Victor\textsuperscript{7} reported transverse myelopathies in approximately 5 per cent of their cases. Ginsburg\textsuperscript{6} reported invasion of the central nervous system in 10 of 36 cases and Weil\textsuperscript{17} reported that 14 per cent of patients with Hodgkin’s disease showed involvement of the spinal cord. Very rarely does direct invasion of the central nervous system occur. When it does it is usually of the sarcomatous type and metastatic in origin.\textsuperscript{19}

Schricker and Smith\textsuperscript{13} reported a case of apparently primary nonsarcomatous intracerebral Hodgkin’s disease in a 45-year-old white male which was proven histologically following surgical removal by Dr. H. G. Schwartz. This patient is alive without signs of recurrence 6 years later. There have never been systemic symptoms or signs of Hodgkin’s disease present.

Fein and Newill\textsuperscript{5} recently reported a case of cerebral invasion by contiguity. Gordon,\textsuperscript{9} in a recent article, stated that Hodgkin’s disease may be present with signs of involvement of the spinal cord as the initial manifestation of the disease.

The other lymphoma that attacks the nervous system frequently is lymphosarcoma. It may affect spinal cord as well as intracranial structures. It may infiltrate the epidural space, causing compression of the spinal cord,\textsuperscript{1} or may invade the cerebral leptomeninges, causing cranial-nerve palsy, headache, and slight rigidity of the neck.\textsuperscript{9}

It is the purpose of this paper to present our experiences with the neurologic complications occurring in 1,264 cases of leukemia and lymphoma seen at the Ohio State University Hospital in a 3-year period from 1954 to 1957, to outline clinically recognizable neurologic syndromes, and to suggest methods of management.

**MATERIAL**

In the past 3 years, the neurosurgical and hematologic services of the Ohio State University Hospital have cooperated closely in the study of all patients suffering from leukemia or lymphoma who showed evidence of
development of lesions of the nervous system. During this period from February 1954 to February 1957, a total of 1,264 cases has been seen. These represent all patients seen at the University Hospital, both old and new, over the 3-year period. Table 1 is a summary of the total number of cases arranged in accordance with the classification used at this institution. The diagnosis of leukemia was made in each instance by examination of peripheral blood and bone marrow. The diagnosis of lymphoma was made in all cases by lymph-node biopsy. The study of the neurologic complications in this group of patients is the material of this investigation.

**TABLE 1**

*Classification of 1,264 patients with leukemia and lymphoma*

*(February, 1954 to February, 1957)*

<table>
<thead>
<tr>
<th>Leukemia</th>
<th>Neurologic Complication</th>
<th>Lymphoma</th>
<th>Neurologic Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Leukemia</td>
<td>No. of Patients</td>
<td>Hemorrhage</td>
<td>Leukemic Infiltration</td>
</tr>
<tr>
<td>----------</td>
<td>----------------</td>
<td>-----------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Acute lymphatic*</td>
<td>145</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Chronic lymphatic</td>
<td>300</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Acute myelogenous</td>
<td>48</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Chronic myelogenous</td>
<td>170</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Monocytic</td>
<td>152</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>815</td>
<td>86</td>
<td>15</td>
</tr>
</tbody>
</table>

* One case of acute mycotic septicemia with meningoencephalitis.

**THE LEUKEMIAS**

Among the 815 leukemias, the most frequent neurologic complication was hemorrhage caused by thrombocytopenia. Eighty-six patients with leukemia expired from bleeding in or about the central nervous system. It is, of course, understood that many other patients who died at home or in other institutions and whose cause of death is unknown also might have died from this complication. The usual pattern has been massive intracerebral, subarachnoid, or intra-axial hemorrhage, associated with severe thrombocytopenia, usually with clinical evidence of hemorrhagic diathesis elsewhere. There were a few instances of subdural hematoma. Such hemorrhages have been invariably fatal within a few hours or days. In no instance did the tendency toward bleeding subside so as to permit any attempt at surgical intervention. We do not, therefore, feel that attempts at operative treatment are justified in the presence of marked depression of platelets.
In contrast, however, 15, or 1.8 per cent, of our patients with leukemia presented several forms of neurologic involvement that are amenable to treatment if diagnosis is prompt.

Table 2 is an admittedly arbitrary breakdown of the syndromes produced by neoplastic cells in or about the nervous system. These are actually variations on a theme, but the clinical manifestations, treatment, and prognosis are sufficiently discrete to justify the proposed division into three types. Some lymphosarcomas have been included here with the leukemias because of the frequent similarity of the pattern of neurologic involvement.

**TABLE 2**

<table>
<thead>
<tr>
<th>Clinical Types</th>
<th>Acute Lymphatic Leukemia</th>
<th>Chronic Myelogenous Leukemia</th>
<th>Monocytic Leukemia</th>
<th>Lymphosarcoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Hydrops&quot; pattern</td>
<td>9</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intra-axial and perineural infiltration</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

I. The "Hydrops" Pattern. The most important variant we have come to call the "hydrops" pattern because the presence of severe increase in intracranial pressure without focal sign or without significant abnormalities in the cerebrospinal fluid spaces as demonstrated by air studies closely resembles the syndrome of benign idiopathic intracranial hypertension, also called "pseudo-tumor" or "hydrops," with which the neurosurgeon is familiar. The effective intracranial mass seems to be the swollen brain, rather than increased volume of cerebrospinal fluid, as in hydrocephalus. For this reason, shunting procedures are relatively ineffectual. The condition ordinarily appeared during periods of activity of the leukemia, but in some cases it became manifest during periods of partial or complete hematologic remission, usually achieved by chemotherapy. In only one instance has it been the presenting symptom in a previously undiagnosed case of leukemia.

The symptoms are usually headache, lethargy, and vomiting. Papilledema is prominent and may progress to secondary optic atrophy and blindness. Seizures are rare. Abducens palsies may develop late, but true focal neurologic deficit does not seem to occur. The condition may persist for weeks (Case 2), and may recur after effective treatment.

Two patients of this group were treated with chemotherapy alone and the neurologic symptoms progressed. Also, a "hydrops" syndrome developed in 2 patients when they were receiving an adequate therapeutic dose and in 5 when receiving a maintenance dose of either Aminopterin, Purinethol and/or steroids. In our hands, roentgen-ray therapy given early in the development of the neurologic complication seems to be rapidly effective in
reversing the neurologic symptoms. In all cases chemotherapy was given together with the roentgen-ray therapy.

In the earlier cases, faced with choked discs, we performed ventriculography and biopsy of the brain. We have since learned to recognize this syndrome by the clinical signs and symptoms, and now begin roentgen-ray therapy at once without recourse to the above procedures.

**Case 1.** C.C., a 17-year-old boy, was admitted with headache, vomiting and papilledema. A diagnosis of acute lymphatic leukemia had been made 3 months previously.

Neurologic findings were negative in all other respects. His neck was supple. At the time of the appearance of the neurologic complication he was on a maintenance therapy consisting of 50 mg. of Purinethol and 50 mg. of Azaserine three times a week.

Blood count on this admission was: total red blood cells 3.34 per c.mm., hemoglobin 10.6 gm. per 100 cc., reticulocytes 0.6 per cent, platelets 334,000 per c.mm., total white blood cells 2,300 per c.mm., with 32 per cent neutrophils, 44 per cent lymphocytes and 24 per cent lymphosarcoma cells. The bone marrow showed marked infiltration by lymphosarcoma cells.

He was treated for 35 days with Aminopterin, beginning with 1.0 mg. daily for 3 days, followed by 0.5 mg. daily, and Purinethol, 100 mg. daily, with no improvement of his neurologic symptoms.

He was then re-admitted. Electroencephalogram showed a mild diffuse 3–5/sec. slowing without focalization. Ventriculograms were done and were normal. The ventricular fluid contained 1,711 cells of the lymphocytic series, 14 mg. per cent of protein, 52 mg. per cent of sugar, and 655 mg. per cent of chloride. Biopsy of the brain showed diffuse infiltration of the leptomeninges and Virchow-Robin spaces with lymphosarcoma cells (Fig. 1). The brain appeared grossly normal in the area from which this specimen was taken. Subtemporal decompression was done and roentgen-ray therapy was instituted at once. He received 1,032 r to the whole brain from two opposite fields in 24 days. He made a prompt clinical recovery.

Four months later he returned with the same symptoms. The decompression was bulging and tense. Ventriculograms were again normal (Fig. 2) and prompt recovery followed a second course of 2,675 r administered to the entire vault over a period of 19 days.

He expired at home 12 months after the first neurologic symptoms in an acute illness in which headache and diplopia were prominent.

**Case 2.** M.F., a 3-year-old boy, began to have fluctuating but increasingly severe headache about 5 months after the diagnosis of acute lymphatic leukemia had been made. When admitted to the University Hospital he was in critical condition, emaciated, blind, and semistuporous.

The head was slightly enlarged, and the sutures of the cranial vault were widened (Fig. 3). His neck was supple. There was severe chronic papilledema with secondary optic atrophy. At the time of the appearance of the neurologic complications he was on maintenance therapy consisting of 0.5 mg. of Aminopterin twice a week.

The blood count on admission was: total red blood cells 2.31 per c.mm., hemoglobin 7.9 gm. per 100 cc., reticulocytes were not seen, platelets were not seen, total white blood cells 57,000 per c.mm., with 4 per cent neutrophils, 59 per cent eosino-
Fig. 1. Case 1. Photomicrograph of biopsy of brain, showing infiltration of leptomeninges and Virchow-Robin spaces with lymphosarcoma cells.

Fig. 2. Case 1. Ventriculogram, following right subtemporal decompression
phils, 7 per cent lymphocytes, and 30 per cent lymphosarcoma cells. The bone marrow showed marked infiltration by lymphosarcoma cells and eosinophils.

Roentgen-ray therapy was instituted at once, and he received a total tumor dose of 900 r to the whole skull by parallel opposing fields, in a period of 10 days. The Aminopterin was increased to 0.5 mg. daily and he also was started on Prednisone, 20 mg. daily. Within 4 days, the child was alert, cheerful, and eating well.

Although he remained essentially blind, he was active and free of symptoms for 9 months. Then within 5 days, there developed rapidly progressive ataxia, lethargy, and vomiting. Terminally, he was in continuous ocuuglyric crisis. A very coarse nystagmus appeared whenever he was turned to the left side, and he would cry and show signs of distress, sometimes vomiting. He expired after 9 days.

Fig. 3. Case 2. Roentgenogram of skull, showing enlargement of the head and separation of sutures caused by increased intracranial pressure of 5 months' duration.

At autopsy, there was severe leptomeningeal and perivascular leukemic infiltration with lymphosarcoma cells, and there were scattered areas of encephalomalacia. The ventricles were not dilated. Similar changes were noted in the spinal cord and its coverings.

Case 3. C.E., a 55-year-old white male, had had chronic myelogenous leukemia for 11 years previous to the appearance of his neurologic symptoms. During these years he was given roentgen-ray therapy over the spleen, radioactive phosphorus (P-32) and Purinethol. Splenectomy was performed 4 years before admission.

His neurologic symptoms consisted of headaches, nausea, vomiting and papilledema. At the time of the appearance of the symptoms, he was on 50 mg. of Purinethol daily. The peripheral blood count was: total red blood cells 3.71 per c.mm., hemoglobin 11.0 gm. per 100 cc., platelets 685,840, reticulocytes 1.8 per cent, total white blood cells 28,100, with 50 per cent polymorphonuclear neutrophils, 2 per cent myelocytes C, 8 per cent myelocytes B, 34 per cent myeloblasts, 4 per cent lymphocytes and 2 per cent monocytes. Hematologically he was in a blastic stage of his chronic myeloid leukemia.
He was treated with 3.0 mc. of radioactive phosphorus (P-32) and Purinethol, but no improvement of his neurologic symptoms was obtained after 2 weeks.

Spinal puncture yielded a slightly turbid fluid under a pressure of 270 mm. of cerebrospinal fluid containing 58 red blood cells, 116 lymphocytes, 52 mg. per cent sugar, 43 mg. per cent protein and 722 mg. per cent chlorides. Electroencephalogram showed a mild diffuse slowing. Ventriculograms were normal. Biopsy of the brain was unsatisfactory. Roentgen-ray therapy was immediately instituted and he received 1,000 r to the skull. He made a prompt clinical recovery.

He expired 1 month later from acute bronchopneumonia.

Comment. While most frequent in acute lymphatic leukemia (9 of 145 cases), this syndrome is also seen in lymphosarcoma (3 of 87 cases) and other leukemias (1 of 152 monocyctic leukemias and 1 of 170 chronic myelogenous leukemias).

Since our first case (Case 1) we have not resorted to surgical treatment; roentgen-ray therapy has proven rapidly effective in most cases. The dosage recommended is around 2,000 r tumor dose to the entire brain given through opposing lateral ports of the skull as soon as clinical signs of headache, lethargy, meningismus, or papilledema develop in the leukemic patient.

There is no discernible relationship between the appearance of this complication and the type of chemotherapy received by the patient, or to evidence of activity of the disease in the peripheral blood or bone marrow. Attempts to control the infiltrations of the brain by increasing doses of Aminopterin and 6-mercaptopurine alone have usually failed in our hands; however, we have increased the dosage of chemotherapeutic agents routinely when the neurologic symptoms appear.

II. Hydrocephalus. Communicating hydrocephalus has been seen in only one instance in this series.

Case 4. G.S., a 3-year-old boy, was admitted with lethargy, vomiting, a bilateral abducens palsy and blindness. A diagnosis of acute lymphatic leukemia had been made 8 months previously. The diagnosis of the “hydrops” syndrome was made in spite of the absence of papilledema. At the time of the appearance of the neurologic complications he was on Purinethol, 50 mg. daily, Aminopterin, 0.5 mg. every third day, and Prednisone, 5.0 mg. daily. At this time he was in a hematologic remission. Peripheral blood count was: total red blood cells 4.78 per c.mm., hemoglobin 13.3 gm. per 100 cc., reticulocytes 1.8 per cent, platelets 1,577,400 per c.mm., total white blood cells 8,250 per c.mm., with 72 per cent neutrophils, 18 per cent small lymphocytes and 10 per cent monocytes. The bone marrow was of normal cellularity and content, and no lymphosarcoma cells were seen.

Roentgenograms of the skull showed diastasis of the sutures. Roentgen-ray therapy was given, a total tumor dose of 1,000 r to the whole skull, but without improvement. Lumbar puncture yielded clear fluid under pressure of 600 mm. of cerebrospinal fluid, containing 222 lymphocytes per c.mm., a total protein of 32 mg. per cent, and sugar of 41 mg. per cent.

Ventriculograms (Fig. 4) at this time showed a marked symmetrical ventricular dilatation with little air in the basal cisterns. A ventriculojugular shunt was performed with the Holter valve. The child responded immediately and was asympto-
matic within a week, except for persistent blindness. His abducens palsies cleared. He remains active and comfortable at this writing, 5 months postoperative. The valve is still functioning well.

*Comment.* It would seem from this case that evidence of increased intracranial pressure without papilledema that fails to respond to roentgen-ray therapy should arouse suspicion that hydrocephalus exists. The optic nerves have not had time to become atrophic, and it is presumed that the discs do not choke because the subarachnoid spaces about the optic nerves are obliterated and do not transmit pressure. Something similar to this used to be a familiar occurrence in tuberculous meningitis, when heavy basilar exudate produced severe intracranial pressure and hydrocephalus for long periods without papilledema.

Control of the systemic disease is good enough today to warrant palliative surgery in the form of shunting procedures.

**III. Intra-axial and Perineural Infiltration.** Intra-axial infiltrations have also been uncommon, but have occurred in many forms, from peripheral neuropathies and multiple cranial-nerve palsies to signs of intra-axial destructive lesions. Response to roentgen-ray therapy has been variable, but, in general, fairly good.

*Case 5.* P.A., a 61-year-old white female, entered University Hospital 1 month after the onset of severe low-back pain radiating to the tip of the sacrum and both thighs posteriorly. She had been hospitalized elsewhere, and an abnormal blood count was found on routine examination.
There was tenderness to percussion over the upper lumbar spine. Hyposthesia was demonstrated from S1 to S5 on the right, and S2 to S5 on the left. Ankle jerks were absent, and the left knee jerk was less active than the right.

The peripheral blood on admission was: total red blood cells 2.78 per c.mm., hemoglobin 9.2 gm. per cent, reticulocytes 4.4 per cent, platelets 2,280,000, total white blood cells 148,000 per c.mm., with 70 per cent polymorphonuclear neutrophils, 4 per cent myelocytes C, 18 per cent basophils, 6 per cent eosinophils, and 2 per cent monocytes. Examination of bone marrow obtained by aspiration revealed a hyperplastic marrow with slight shift of the myeloid series to the left and a marked relative and absolute myeloid hyperplasia.

Roentgenograms of the chest, spine, and pelvis were not remarkable.

Lumbar puncture was attempted, but fluid could not be obtained. Six ml. of Pantopaque were then injected into the cisterna magna, and a complete block of the subarachnoid space was demonstrated in the region of L2. The obstruction was irregular, spread over 2 or 3 cm., and gave the appearance of arachnoiditis. There was evidence of thickened nerve roots near the level of obstruction.

Roentgen-ray therapy was started over this area, and within 4 days the pain had largely disappeared, but the patient continued to complain of perineal numbness and tingling. No other therapy was attempted, since the white blood cell count after the roentgen-ray therapy was adequately reduced to 18,000 per c.mm. over a period of 2½ weeks.

Comment. At the time of this writing, the sensory deficit has not cleared, and it is too soon to judge the outcome. It is presumed that the process was an infiltration of the roots of the cauda equina by leukemic cells. We feel quite certain that the lesion was not extradural.

SUMMARY

The leukemias and lymphosarcoma produce a variety of neurologic syndromes which are all based upon infiltration of the central nervous system and meninges in one way or another. The most common of these, the "hydrops" pattern, is quite sensitive to roentgen-ray therapy. Hydrocephalus may occur, and calls for shunting procedures. Intra-axial and intraneural infiltrations carry a worse prognosis and respond less consistently to roentgen-ray therapy. Chemotherapy alone has been relatively ineffective in controlling the neurologic complications of the leukemias, but will control the systemic aspects of the disease.

HODGKIN'S DISEASE

The neurologic complications of Hodgkin's disease present a somewhat different problem. Over the 3 years covered by this survey, 257 patients with Hodgkin's disease have been seen, either as new or returning patients, in our clinic.

Of these, 3, or 1.2 per cent, have had neurologic complications caused by thrombocytopenic hemorrhage. We can simply repeat the statements made about the leukemias: hemorrhagic complications are not amenable to surgical treatment. Possibly the incidence of this terminal event would be higher if deaths occurring at home and in other institutions were included.
NEUROLOGIC COMPLICATIONS OF LEUKEMIAS

Thirteen, or 5 per cent, of the group have had neurologic complications caused by Hodgkin’s granuloma invading or compressing the nervous system. The “hydrops” syndrome of diffuse perivascular infiltration has not been seen, but mass lesions and certain obscure syndromes have appeared in seemingly increasing numbers as medical treatment has increased the life expectancy in this disease.

Table 3 is an arbitrary breakdown of the neurologic syndromes produced by Hodgkin’s disease. One patient with lymphosarcoma has been included in this group because of the similarity of the pattern of neurologic involvement.

I. Spinal Extradural Granuloma. This lesion, long familiar to neurosurgeons, remains the most common cause of neurologic symptoms in Hodgkin’s disease. We feel that the exercise of rather fine judgment is required in the management of these cases for optimal results at minimal risk. Surgery can often be avoided by close cooperation between the internist, radiotherapist,

<table>
<thead>
<tr>
<th>TABLE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Types</td>
</tr>
<tr>
<td>Spinal extradural granuloma</td>
</tr>
<tr>
<td>Intracerebral tumor</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

and neurosurgeon when the neurologic deficit is incomplete. If function is nearly or entirely gone, surgery is the only treatment fast enough to be satisfactory.

Accurate localization of the lesion is of first importance, followed by prompt treatment to relieve the pressure on the spinal cord. As a rule, we have used myelography for the precision in localization that it offers.

Case 6. R.M., an 18-year-old white male, was admitted complaining of difficulty in walking. The diagnosis of Hodgkin’s disease had been made 1 year previously.

On admission his temperature was normal, there was no remarkable lymphadenopathy, and spleen and liver were normal. The peripheral blood and bone marrow were normal. Positive neurologic findings were absent abdominal reflexes, bilateral positive Babinski sign, and bilateral abortive ankle clonus. The knee jerk was decreased on the left, and there was marked weakness of dorsiflexion in both feet. Hypesthesia in L3, L4 and L5 coincided with his complaints of radiating pain into the legs. Myelography showed a complete block at the dorsoolumbar interspace and a partial block at L4–5. Spinal puncture at L3 released a clear fluid under a pressure of 230 mm. cerebrospinal fluid, containing 140 mg. per cent protein, 750 mg. per cent chlorides, 70 mg. per cent sugar, and 3 lymphocytes; serology was negative, colloidal gold was 111221000, and spinal cultures were negative. The diagnosis of two extradural Hodgkin’s tumors was made, one causing a complete block at D12 and the other a partial block at L4 and L5.
Roentgen-ray therapy was started over the lower dorsal spine and 3 days later over the L3–S1 segments. After the third dose of roentgen rays, the neurologic symptoms improved markedly. He received a total tumor dose of 2,000 r over each area. The patient is doing well at present, he has had no recurrence of the symptoms of Hodgkin's disease, or neurologic symptoms, after 1½ years of observation.

Comment. This case illustrates a rather common pattern of spinal extradural granuloma seen in Hodgkin's disease, successfully treated with roentgen-ray therapy.

Case 7. D.S., a 50-year-old white female, was first seen with extreme pain radiating down the right leg. She had been operated upon 6 months before, and again 3 weeks before at another institution for "herniated disc." There were two superficial draining sinuses at the lower end of her recent laminectomy wound. Because of her extreme pain and findings of L5 and S1 radiculopathy, the diagnosis of pyogenic granuloma of the extradural space was made. She failed to improve on antibiotics and rest, became completely demoralized and required large doses of morphine. On May 20, 1955, the wound was explored, only heavy scar tissue was found, and a dorsal rhizotomy of L5 and S1 was performed.

She improved markedly, but after 6 months returned with similar pain, but on the opposite side. Myelography (Fig. 5A) showed a filling defect at the L5–S1 interspace on the left side. At operation, the fourth procedure on the lumbar spine, granulomatous tissue was excised and the histologic report was "nonspecific granulomatous tissue," but the possibility of Hodgkin's disease was considered by the pathologist. She received 2,000 r tumor dose to the lumbar spine in 2 weeks' time postoperatively with excellent clinical response.

She was again symptom free for 3 months, at which time she was re-admitted with root pain localized in D9, right, and a progressive spastic quadriplegia. Myelography at this time showed a defect at D9 (Fig. 5B), right, and a complete block at C7 (Fig. 5C). Inasmuch as she was still able to walk, we thought that irradiation of the known sites of disease was the treatment of choice. She received 2,000 r tumor dose over each site. Essentially complete remission was again obtained, and the patient has remained symptom free for 19 months, as of this writing. The myelogram has been rechecked with the Pantopaque left in for that purpose (Fig. 5D).

In October 1956, a mass, which measured 3×2 cm., was noted in the left cervical region. This node was removed surgically and the histologic diagnosis was Hodgkin's sarcoma. She received roentgen-ray therapy locally with prompt resolution of the mass.

Comment. This rather unusual case illustrates the bizarre manifestations of the disease and its excellent palliation by roentgen-ray therapy. The presence of subarachnoid block does not, per se, require surgical decompression when localization is precise. Pantopaque may be left in the spinal canal so that the progress of the lesion may be followed if necessary.

II. Intracerebral Tumor. The same general principles apply to intracerebral mass lesions: First, accurate localization; second, roentgen-ray therapy started at very low dosage (50 to 75 r) in order to avoid initial edema of the tissue. Scrupulous neurologic observation during therapy is imperative; third, prompt surgical intervention should the patient fail to respond, or become worse.
Case 7. (A) Filling defect at L5, S1, left. Evidence of previous exploration at L5, S1, right. (B and C) Filling defect at D9, right, and complete block at C7. (D) Control myelography following roentgen-ray therapy, showing resolution of block.

Case 8. E.C., a 20-year-old white male, had suffered from Hodgkin’s disease for 4 years when he began to have severe headache, a rapidly progressive right hemiparesis, hemianopsia, and mixed sensory aphasia, with severe papilledema. The electroencephalogram was abnormal and suggested a left temporofrontal mass and diffuse increase in intracranial pressure. The diagnosis of intracranial tumor was made. In view of the thrombocytopenia present, surgery was considered inadvisable. Roentgen-ray therapy to the left temporoparietal region was begun at once. He reached the lowest ebb on the 5th day, when the left pupil dilated and the pulse slowed to 48. Complete neurologic recovery ensued.

His death 2 months later was caused by pulmonary infiltration by Hodgkin’s disease. Fig. 6 shows the remains of the Hodgkin’s tissue in the wall of the scarred, cystic area found in the left temporoparietal region. There was some dilatation of the underlying ventricle, indicating a contraction of the previously involved area.
Comment. As a rule we would recommend surgery for a lesion this far advanced. The patient very nearly expired before the lesion began to regress under roentgen-ray therapy. Inasmuch as his low platelet count would not permit surgery, however, we had no choice. The case serves to point up what may be expected of roentgen-ray therapy for this condition.

III. Miscellaneous. The third group of neurologic complications in Hodgkin's disease is a heterogeneous group, the precise nature of which has not always been established. It may include some cases of Torula histolytica infection, although we have been unable to prove this. We have seen one intra-axial tumor mass, and one case in which myelography showed a picture suggestive of arachnoiditis. This young woman had had extensive irradiation about the root of the neck and showed signs of involvement of the brachial plexus (Tinel's sign), probably the cervical roots, and the long tracts passing through the cervical cord. All changes could be explained on the basis of roentgen-ray reaction.

On the other hand, we have also seen manifestations of intra-axial disease in which cerebrospinal fluid and contrast studies have been normal. Fig. 7 is a summary of one such problem in a 31-year-old woman, who unfortunately expired at home without autopsy.
In general, this last group of cases have in common the fact that the physician must rely chiefly on the neurologic examination, since roentgen-ray findings are often absent. Irradiation is the treatment of choice when the lesion can be localized clinically, and if there is reasonable assurance that the lesion is not caused by postirradiation changes in the first place. Chemo-therapeutic drugs, HN2, TEM, or CB-1348, have been of help in some patients of this group.

FIG. 7. Summary of fluctuating neurologic pattern in a 31-year-old female with Hodgkin's disease. Myelograms on two occasions were normal. Stippled areas indicate relative touch deficit, hatched areas represent analgesia.

DISCUSSION

In spite of sporadic reports and reviews over many years, it is difficult to obtain a clear-cut picture of the pathophysiologic changes in the central nervous system caused by leukemia and lymphoma. Inasmuch as these changes must be understood for proper direction of therapy, we have attempted to set up a classification based on clinical considerations.

The leukemias most frequently invade the leptomeninges and Virchow-Robin spaces in such a manner as to produce increased intracranial pressure caused by the increased mass of the brain, without localized mass lesions, hydrocephalus, or focal neurologic dysfunction. We have compared this to the syndrome of benign idiopathic intracranial hypertension, or "hydrops," because of the normal air studies in the presence of increased intracranial pressure. The electroencephalogram usually shows a mild diffuse abnormality. Biopsy of the brain is diagnostic but unnecessary. Spinal fluid findings may be diagnostic. They consist of an increased pressure and pleocytosis of up to 2,000 cells, usually called lymphocytes. Supravital studies of these cells show them to be leukemic cells. Determinations of sugar in the
spinal fluid have usually been in the normal or low-normal range, although subnormal levels have been seen. Sugar levels do not appear to be a function of the pleocytosis, as indicated by Goldring and Harford,\textsuperscript{3} since a sugar level of 52 mg. per cent has been seen, with 1,711 cells per c.mm., and 9.4 mg. per cent of sugar, our lowest reading, was in a spinal fluid containing 740 cells.

In early cases, when there is doubt of the diagnosis, the cell content of the spinal fluid seems to be the best diagnostic criterion, especially with the aid of supravital techniques.

Roentgen-ray treatment has been most effective in our hands. We do not recommend surgery for this type of neurologic complication. Although subtemporal decompression (Case 1) appears to be a rational approach, it is rarely necessary. We have increased regularly the dosage of chemotherapeutic agents while giving roentgen-ray therapy but do not subscribe to the opinion of Wells and Silver\textsuperscript{18} that drugs alone will control this complication. Indeed, our experiences with the appearance of this syndrome in the face of maintenance of even therapeutic doses of chemotherapeutic agents, and its failure to respond to therapeutic doses, suggests the reverse. We have speculated that these drugs may not cross the blood-brain barrier, and have felt that the increasing frequency of this condition may be a result of successful control of the systemic aspects of the disease, permitting the neurologic infiltration to occur in an area to which the drug does not gain access. We have not used intrathecal chemotherapeutic agents.

Hydrocephalus and the more massive infiltration of brain stem, cord, and roots have been discussed with the case reports. They are relatively rare.

Lymphosarcoma has been included under leukemic complications and also with Hodgkin's disease because of its bivalent clinical behavior. We have seen the hydrops syndrome and also mass lesions behaving like Hodgkin's disease or other metastatic malignancy. This seems consistent with the basic character of the lymphosarcoma, which in advanced stages invades the blood like an acute lymphatic leukemia.

Hodgkin's disease is a more familiar problem, especially the spinal extradural granuloma. Intracerebral mass lesions are certainly possible and are managed similarly. Roentgen-ray therapy has been the treatment of choice. Nitrogen mustard is also effective in the control of the extradural granulomas; however, we have gained the impression that the response to local roentgen-ray therapy is more rapid and lasts longer. We have come to use both agents at the same time for maximal efficacy, if the patient's general condition and hematologic picture will tolerate the use of nitrogen mustard.

There remain to be explained certain bizarre neurologic syndromes, obviously intra-axial and/or intraneural, in which we lack autopsy material. Some of these may be infectious, some the result of vascular changes following roentgen-ray therapy, and some are certainly caused by intra-axial infiltration. The latter group in the brain stem and cord have been found at
NEUROLOGIC COMPLICATIONS OF LEUKEMIAS

operation and at autopsy. Response to mustards and roentgen rays in some of these undiagnosed neurologic syndromes associated with Hodgkin's disease has been only fair at best. The danger of treating a postirradiation myelopathy with further radiation must be borne in mind since the neurologic symptoms often appear 3 years or so after the radiation therapy.

SUMMARY

1. The neurologic complications encountered over a 3-year period in 1,264 cases of leukemia and lymphoma have been reviewed.

2. Characteristic syndromes are described and suggestions are offered as to their management.

The authors wish to thank Doctor Charles A. Doan and Doctor Bruce K. Wiseman for their assistance in this work and for the opportunity to study patients under their care, and Doctor Henry E. Wilson and Doctor Robert L. Wall for the use of their cases.

REFERENCES


