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PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY*

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IN the course of the regular post-mortem examination of the brains of patients coming to autopsy at the Massachusetts General Hospital, my attention has been called in recent years to an unusual disorder of the cerebral white matter with distinctive features unfamiliar to me and my colleagues from our own experience or that of others. We reported 3 such cases in 1958[1] and called the condition "progressive multifocal leukoencephalopathy" to emphasize the outstanding clinicopathological features. Since these 3 cases, and 3 of the 5 others previously reported, were associated either with lymphatic leukemia or with Hodgkin's disease, we considered the disorder to be a hitherto unrecognized complication of these diseases, although we realized that it might occasionally occur under other conditions. We were unable to offer any suggestions about its cause. Since then, our experience with it has been considerably broadened by the acquisition of new material, so that our previous statements now require some modification.

CASE REPORTS

CASE 1‡ (M.G.H. 01-72-58; autopsy 16159). A 71-year-old woman had had chronic lymphatic leukemia for 16 years. About 4 months before death, a gradually progressive left-sided hemiparesis appeared, followed by insidiously developing disorientation, confusion and blindness, and, terminally, hemiparesis on the right side. On repeated lumbar punctures, the cerebrospinal fluid was normal in all respects, except for 25 lymphocytes per cubic millimeter in a sample taken shortly before death.

Post-mortem examination confirmed the diagnosis of chronic lymphatic leukemia. In the brain there were extensive demyelinative lesions of the white matter of the cerebral hemispheres, which on the right extended from the occipital to the frontal pole and on the left were confined to the occipital lobe. The deep structures of the brain, and the cerebellum and brain stem, were free of lesions. Microscopically, the pathologic process was characterized by the occurrence of innumerable minute foci up to about 1 mm. in diameter that coalesced to form the large macroscopic lesions. Within the lesions myelin sheaths were absent, and there were numerous macrophages containing the intensely sudanophilic lipid droplets typical of myelin breakdown. Axis cylinders were relatively spared; thus, the process may accurately be called demyelinative. In many of the lesions there were dense accumulations of lymphocytes in the perivascular spaces. In addition to these findings, which are commonly observed in demyelinative lesions, there were certain wholly unfamiliar cell changes. In the first place, many of the astrocytes in the larger lesions were gigantic in size, with irregular or multiple nuclei containing dense masses of chromatin and, occasionally, mitoses, some of which were multipolar. Secondly, at the periphery of the lesions there were numerous smaller cells with round, densely basophilic nuclei that often contained eosinophilic inclusions. We identified these cells as oligodendrocytes, and considered that they were undergoing an alteration not previously described.

CASE 2 (M.G.H. 91-21-38; autopsy 19024). A 73-year-old woman had had chronic lymphatic leukemia for 5 years. Four months before death she became irritable and depressed and complained of difficulty in concentrating. In the ensuing months a progressive right-sided hemiparesis and aphasia developed, followed by a homonymous hemianopsia on the right side and, eventually, blindness and complete dementia. The most significant finding among the numerous laboratory investigations was a normal cerebrospinal fluid.

Post-mortem examination showed widespread changes typical of chronic lymphatic leukemia. In the brain there were multiple bilateral lesions of the same character as in Case 1. In the present case they were particularly numerous in the deep layers of the cortex and the subcortical white matter. The central nuclei of the cerebral hemispheres as well as the brain stem and cerebellum contained many lesions, and there was a large, confluent focus (where the disease appeared to be farthest advanced) in the left parietal region. Gigantic astrocytes (but without mitoses) and the distinctive alteration of oligodendrocytes were abundantly evident. There were no perivascular lymphocytic infiltrations. Although the granule-cell layer of the cerebellar cortex showed poor preservation of cell structure as a result of either terminal or post-mortem changes, recent review of the sections has shown in this layer a remarkable cytologic alteration that was first recognized in Case 8, and is described with the post-mortem findings in that case.

CASE 3§ (Emory University Hospital, Case 61-707U; autopsy A54-155; M.G.H. Neuropath. Lab. acc. no. X-165). A 42-year-old man was found to have Hodgkin's disease about 10 months before death. In the last 3 months of life, progressive aphasia and right-sided weakness developed, followed by confusion and, finally, coma. On post-mortem examination, changes typical of Hodgkin's disease were found in many organs. In the white matter of both cerebral hemispheres there were numerous lesions, most abun-

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‡Cases 1, 2 and 3 were those previously reported.[1] They are briefly summarized here for the sake of completeness.

§Reported through the courtesy of Drs. Herbert R. Karp, Walter H. Sheldon and Heinz Bauer, Emory University School of Medicine, Georgia.

dant in the left parietal region. Microscopically, they were identical to those in Cases 1 and 2 although giant astrocytes were rare. There were no perivascular lymphocytic infiltrations.

CASE 4* (M.G.H. autopsy 21550). A 65-year-old railroad man came to medical attention in December, 1955, because of fever and unexplained anemia. A sternal-marrow biopsy showed chronic myelogenous leukemia. He was admitted on numerous occasions to the Emerson Hospital because of fever and anemia, and was repeatedly found to have pneumonia. Treatment consisted of transfusions, antibiotics and, at various times, busulfan† and prednisone. There had been no neurologic abnormalities until mid-September, 1958, when "morning confusion and slurring of speech with asymmetry of the face and weakness of the left arm and leg" suddenly appeared. He became emotionally labile to an increasing degree, with silliness, inappropriate laughter and some tearfulness, and died in coma on January 11, 1959.

Post-mortem examination showed increased cellularity of the bone marrow, with a predominance of myeloid elements, characteristic of chronic myelogenous leukemia. In the brain multiple lesions, generally 1 to 3 mm. in diameter, but with some larger, confluent foci, were present in the subcortical white matter and deep cortical layers in the right frontoparietal region. There were a few similar lesions in the left cerebral hemisphere and in the midbrain. Microscopically, these were of the same multifocal, demyelinative character as in the previous cases. Giant astrocytes, however, were absent, and altered oligodendrocytes were scarce. Perivascular lymphocytic infiltration within or adjacent to the lesions was frequent, and this case was unique in that many scattered plasma cells were located within the lesions.

CASE 5‡ (Royal Perth Hospital, autopsy A59/270). A 49-year-old man was seen in neurologic consultation because of weakness of the right arm of about 6 weeks' duration. Some 2½ years previously he had been found to have splenomegaly and widespread lymphadenopathy; biopsy of a cervical lymph node disclosed lymphosarcoma. Subsequently, he was given radiation therapy, with an excellent clinical result. A relapse occurred 6 months before the final admission, for which he was treated first with nitrogen mustard and then, because of evidence of hemolysis, with prednisolone. There was a satisfactory response to this regimen. A recurrence of anemia 2 months later was treated with further radiation therapy to the spleen and transfusions. Shortly afterward, weakness of the right arm appeared. On neurologic examination 6 weeks later he was vague in giving his history, and "he veered inexplicably from apprehensive depression to inappropriate jocularity." He was, however, fully oriented and co-operative. There was flattening of the right nasolabial fold and severe flaccid weakness of the right arm, without sensory changes. The tendon reflexes were decreased in the right arm but brisk elsewhere; the plantar reflexes were normal. The cerebrospinal fluid was normal in all respects. His state gradually deteriorated. Within 3 weeks after the initial neurologic consultation, the weakness of the right arm had become spastic, with exaggerated reflexes. Replies to sensory examination were unreliable. Testing showed defects in memory and judgment and in calculating ability. An electroencephalogram was diffusely abnormal, with somewhat more pronounced changes on the left. Dysarthria and an obvious aphasia then developed. He died about 3 months after the onset of the neurologic illness.

Post-mortem examination showed severe right-upper-lobe pneumonia. There was little gross evidence of lymphoma, but it was found microscopically in the liver, spleen, paraaortic lymph nodes and bone marrow. Neuropathological examination disclosed multiple bilateral demyelinative lesions in the deep cortical layers and in the subcortical white matter, generally about 1 to 3 mm. in diameter but with many confluent foci, most numerous in the frontal and parietal lobes. A few small lesions were present in the central nuclei of the cerebral hemispheres; there were none in the cerebellum, brain stem or spinal cord. Microscopically, the lesions were typical. The characteristic alteration of oligodendrocytes was conspicuous; many of the affected cells contained eosinophilic intranuclear inclusions. There were frequent gigantic astrocytes. Perivascular lymphocytic infiltrations were absent.

CASE 6§ (V.A.H., Portland, Oregon, autopsy 56A269; AFIP acc. no. 311170; M.G.H. Neuropath. Lab. acc. no. X-227). A 31-year-old man was found in 1949 to have a mediastinal mass on a routine survey film of the chest. Biopsy of an enlarged supraclavicular lymph node in 1950 showed Hodgkin's disease. During the next 4 years he received graded radiation therapy to multiple visceral sites. Brief courses of nitrogen mustard treatment were given in April, 1955, and April, 1956, followed on each occasion by a decrease in the size of the tumor masses. In May, 1956, he complained of blurred vision. Examination showed homonymous blindness in the right lower quadrant that later progressed under observation to a complete homonymous hemianopsia on the right side. There was also a right-sided hemiparesis, most pronounced in the face. The plantar reflex was bilaterally extensor, more strongly on the right. Lumbar puncture showed a normal pressure and a cerebrospinal-fluid protein of 22 mg. per 100 ml. An electroencephalogram disclosed a bilateral occipital slow-wave abnormality. Soon afterward, left-sided cerebellar ataxia gradually developed, and he became blind — with normal optic disks and pupils that reacted sluggishly to light. In July and August, 1956, radiation therapy was given to the occipital regions bilaterally. A pneumoencephalogram done at this time showed a suggestion of a greater than normal amount of air over the occipital lobes. His condition declined in all respects. Terminally, generalized vesicles typical of herpes zoster appeared. He died on December 18, 1956.

Post-mortem examination showed widespread involvement of lymph nodes and viscera by Hodgkin's granuloma. In the brain there were extensive lesions of both cerebral hemispheres, especially in the posterior parts, somewhat more on the left, histologically of the same character as in the other cases. No giant astrocytes were found, however. There were a few scattered perivascular lymphocytic infiltrations.

CASE 7¶ (M.G.H. 02-22-75; autopsy 9479). An 82-year-old man had been frequently seen at the Massachusetts General Hospital since 1922, mainly because of hypertension (blood pressure of 190/100), chronic congestive heart failure and angina pectoris. With limitation of activities, digitalis, nitroglycerin and careful dietary regulation he remained for years relatively untroubled by his illnesses and worked regularly. In about mid-January, 1940, friends noticed that he had become mentally slower than before and that his speech was slurred. On their advice he entered the hospital on February 2, 1940. Examination showed mild congestive heart failure. Neurologically, he was responsive and co-operative, but speech was slurred and there was some slight weakness of the left side of the face and tongue. Tendon reflexes were relatively more active in the left arm than elsewhere, but no other abnormal neurologic findings were described. Routine admission blood examinations gave normal results. He soon became febrile, his general state worsened, and he died on February 15.

Post-mortem examination showed severe coronary atherosclerosis, with acute thrombosis and healed myocardial infarction, together with acute bronchopneumonia and healed apical pulmonary tuberculosis. There was nothing to sug-

*I am indebted to the patient's physician, Dr. L. P. Houck, Concord, Massachusetts, and the Medical Records Department, Emerson Hospital, Concord, who made the clinical notes in this case available.

†In the form of Myleran, Burroughs Wellcome and Company, Tuckahoe, New York.

‡I am indebted to Dr. Mercy Sadka, neurologic consultant to the Department of Medicine, University of Western Australia, Perth, W.A., for the clinical and pathological findings in this case, as well as a generous assortment of excellent stained sections of the brain.

§I am indebted to Dr. James Austin, Division of Neurology, University of Oregon Medical School, Dr. Ernest J. Losli, chief of Laboratory Service, Veterans Administration Hospital, Portland, Oregon, and Colonel Frank M. Townsend, director, and Dr. Webb Haymaker, chief, Neuropathology Section, Armed Forces Institute of Pathology, Washington, D. C., for permission to publish this case, and for clinical notes and pathological material generously placed at my disposal.

¶This case, which had been classified as "encephalitis, type undetermined," was recently discovered by chance in a review of some microscopical material in the Department files.

gest leukemia, lymphoma or a granulomatous inflammatory disease. The brain was unremarkable to naked-eye examination. Microscopically, there were numerous focal demyelinative lesions in the cerebral hemispheres, cerebellum and brain stem. Giant astrocytes were frequent, and a multipolar mitotic figure was found in one of them. There were many typically altered oligodendrocytes. Perivascular lymphocytic infiltration was unusually pronounced.

CASE 8* (St. Mary's Hospital. Waterbury, Conn., autopsy A-16-58; AFIP acc. no. 927316; M.G.H. Neuropath. Lab. acc. no. X-258). A 42-year-old man lived about 2 years after the diagnosis of chronic granulocytic leukemia had been established. For most of the 1st year, he was treated with busulfan. Because of failure of response during the 2d year, treatment was changed to 6-mercaptopurine and prednisone. In addition, he received numerous blood transfusions. Despite his illness, he was able to work until about 3 weeks before death, when he began having vertigo, with a tendency to fall to the left. This was followed by apathy and repetitious speech. Several days before death a left-sided hemiparesis appeared.

Post-mortem examination showed findings typical of chronic granulocytic leukemia. Lesions of the type encountered in the other cases were present in both cerebral hemispheres, more on the right, and in the cerebellar white matter. Microscopically, the lesions showed characteristic oligodendroglial and astrocytic changes, with no perivascular lymphocytic infiltrations. In the cerebellum, there were lesions not previously seen in any case of this series. These consisted of foci of destruction of the granule cells of the cerebellar cortex, varying from microscopical size to 0.5 to 1.0 mm. in diameter. Some were continuous with typical demyelinative lesions in the cerebellar white matter. Within and at the margins of these cerebellar cortical lesions were numerous round or slightly oval cell nuclei with abundant chromatin granules, but without stainable cytoplasm even in fields where the processes of astrocytes were visualized by the Cajal-gold-sublimate method.† These nuclei occurred in groups or clusters in a manner suggesting the normal cytoarchitecture of the granule-cell layer of the cerebellar cortex. They were, however, larger than the granule cells. The largest, with a diameter about twice that of a normal granule cell, were located in the more central parts of the lesions. More peripherally, they resembled more and more closely the normal granule cells with which they were intermingled until at last, in the intact portions of the granule-cell layer, no more could be recognized. Although absolute identification of these cells was not possible, their appearance and distribution suggested that they might be altered granule neurons of the cerebellar cortex.

CASE 9‡ (Presbyterian-St. Luke's Hospital, Chicago, 61688; autopsy A58-158; M.G.H. Neuropath. Lab. acc. no. X-272). A 68-year-old woman entered the hospital on May 12, 1958, complaining of dysphagia, dizziness and nausea of 5 days' duration. Twenty-two months previously a radical mastectomy had been performed for carcinoma of the right breast. Carcinoma was found in some of the excised lymph nodes. Two weeks before the final admission, she began having occasional nausea and dizziness. Dysphagia and diplopia on lateral gaze then developed. On examination the only significant physical finding was nystagmus on lateral gaze. Later, she had counterclockwise vertigo, together with left-lower-facial-muscle weakness, impairment in rapid alternating movements of the right hand and foot and ataxia of the right arm. Treatment consisted of prednisone and general supportive measures. About 1 month before death, an intracerebral injection of a nitrogen mustard analogue was given, without effect on the neurologic abnormalities. Her condition gradually worsened, and she died on July 17.

Post-mortem examination showed the immediate cause of death to be bronchopneumonia. There were multiple foci of metastatic carcinoma in the lungs and mediastinal lymph nodes. In this case the most extensive brain lesions were in the cerebellar white matter and middle cerebellar peduncle bilaterally. The cerebral hemispheres were spared except for a small cluster of lesions in the left parietal region. Abnormal oligodendrocytes of typical appearance were numerous, but giant astrocytes were rare. There were no perivascular lymphocytic infiltrations. In this case, as in Case 8, and as found later in Case 2, there were scattered foci of nerve-cell loss in the granule-cell layer in the cerebellar cortex, and these contained unusual nuclei suggesting enlarged granule neurons.

CASE 10§ (V.A.H., St. Louis, Missouri, autopsy A541; AFIP acc. no. 339069; M.G.H. Neuropath. Lab. acc. no. X-259). Generalized lymphadenopathy developed in this 35-year-old man in 1949, and lymphosarcoma was found. With radiation therapy, nitrogen mustard and cortisone at various times, he remained generally well. On June 26, 1956, he entered the hospital complaining of impaired memory of 1 month's duration. On examination there was generalized lymphadenopathy and enlargement of the liver and spleen. He had difficulty in using words and was slow in answering questions, but there were no other neurologic abnormalities. Lumbar puncture showed normal cerebrospinal-fluid findings. Thereafter, progressively increasing aphasia and right-sided hemiparesis developed, uninfluenced by radiation therapy to the skull and nitrogen mustard. He became unable to swallow and gradually went into coma, dying on September 5.

Post-mortem examination showed widespread involvement of lymph nodes and many organs by lymphocytic lymphoma. In the brain there were diffuse white-matter lesions in both cerebral hemispheres, more extensive on the left, with scattered small demyelinative foci in the brain stem. Microscopically, the lesions were of the same character as in the previous cases. Giant astrocytes were frequent, and many of the abnormal oligodendrocyte nuclei contained eosinophilic inclusions.

DISCUSSION

Ten cases have been presented of a progressive central-nervous-system disorder of relatively rapid course, occurring in nearly each one on a background of a pre-existing chronic disease. In all, the lesions have been typical of what has previously been described as *progressive multifocal leukoencephalopathy*.[1]

To these 10 cases may now be added 12 that have been studied by other workers and either have already been reported or have been prepared for publication. Through the kindness of the investigators concerned, I have been privileged to examine appropriate neuropathological sections from 9 of the 12 and thus have been able to assure myself that the neuropathologic process in each is the same as that seen in the cases described above. In the 3 remaining cases[2,3] the published descriptions and illustrations of the brain lesions leave no doubt of their belonging in this group, and they are so identified by the authors. The entire group of 22 cases is summarized in Table 1.

*I am indebted to Dr. Marcus E. Cox, director, Department of Laboratories, St. Mary's Hospital, Waterbury, Connecticut, and to Colonel Frank M. Townsend, director, and Dr. Webb Haymaker, chief of the Neuropathology Section, Armed Forces Institute of Pathology, Washington, D. C. (who kindly furnished clinical notes and pathological material), for permission to publish this case.

†A considerable number of histologic methods were used in an attempt to demonstrate the shape or cytoplasmic features of these cells, and all failed to do so. The cytoplasm of the cerebellar granule cells was similarly unstained by all these procedures.

‡Material from this case and permission for its publication were generously donated by Dr. Raymond A. Clasen, Department of Pathology, Presbyterian-St. Luke's Hospital, Chicago, Illinois, to whom I am greatly indebted.

§I am indebted to Dr. Howard L. Richardson, chief of Laboratory Service, Veterans Administration Hospital, St. Louis, Missouri, and to Colonel Frank M. Townsend, director, Dr. Webb Haymaker, chief of the Neuropathology Section, and Dr. Richard L. Davis, Armed Forces Institute of Pathology, Washington, D. C., for permission to publish this case and for clinical notes and pathological material.

Clinical Aspects

As shown in Table 1, progressive multifocal leukoencephalopathy is a disease that affects adults of both sexes. The youngest patient died at thirty-one, and the oldest at eighty-two years of age. The average age at the time of death was fifty-seven. Men were affected twice as often as women (15 to 7), but in view of the relatively small number of cases involved, it cannot be stated that this difference is significant.

It has already been pointed out that the neurologic disorder regularly occurs on the background of a preexisting chronic disease. The various associated states are shown in Table 2.

As is now apparent, progressive multifocal leukoencephalopathy must be viewed as a complication of a number of diseases other than Hodgkin's disease or chronic lymphatic leukemia. If Hodgkin's disease, lymphosarcoma and the various forms of leukemia are considered to be neoplastic diseases, 17 of the 22, with the 2 cases of carcinomatosis, were associated with neoplasms. Three of the 5 remaining were cases of granulomatous inflammation (2 of sarcoidosis, 1 of miliary tuberculosis). One of the 2 additional patients (Case 7) had coronary heart disease; the other (Case 2 of Hallervorden[4]) had no known preceding illness.* Both patients were of advanced age (eighty-two and seventy-one years respectively).

TABLE 1. *Summary of the Findings in the Entire Group of 22 Cases.*

SOURCE OF DATA	AGE	SEX	ASSOCIATED DISEASE		NEUROLOGIC DISORDER		OUTSTANDING NEUROPATHOLOGIC FEATURES
			DIAGNOSIS	DURATION	PRINCIPAL MANIFESTATIONS	DURATION	
	yr.						
Hallervorden[4] (1930):							
Case 1 (J.B.)	45	M	Miliary tuberculosis, pulmonary & renal	?	Unsteady gait; dysarthria; dementia; impaired vision; terminally, generalized rigidity.	1 yr.	Widely distributed cerebral lesions, most severe posteriorly; many giant astrocytes.
Case 2 (F.G.)	71	F	?	?	Dementia; generalized choreiform movements; terminally, aphasia.	6 mo.	Lesions more destructive than in Case 1 & principally located in central & occipital regions & basal ganglions; scattered foci in pons & cerebellar white matter; no lesions in spinal cord; many giant astrocytes but fewer than in Case 1.
Winkelman & Moore[5] (1941)	44	F	Hodgkin's disease	18 mo.	Initially: cervical radiculopathy, thought due to local involvement by lymphogranulomatous masses.	(9 mo.)	Extensive lesions, especially in right cerebral hemisphere; typical cell changes.
					Terminally: stupor; left-sided hemiparesis; bilateral pyramidal-tract signs.	< 1 mo.	
Bateman et al.[6] (1945)	43	M	Hodgkin's disease	2 yr.	Progressive visual impairment; dementia; dysarthria; paresis of right arm; right extensor plantar reflex.	2 mo.	Diffuse occipital lesions; typical cell changes.
Christensen & Fog[7] (1955)	59	M	Sarcoidosis	?	Agraphia, alexia & aphasia; visual impairment progressing to blindness; left-facial-muscle weakness; dementia; finally, stupor.	5 mo.	Extensive lesions, partly cavitated, in posterior halves of both cerebral hemispheres; many giant astrocytes.
Cavanagh et al.[2] (1959):							
Case 1	55	M	Hodgkin's disease	5 yr.	Dementia; mild left-sided hemiparesis.	±2 mo.	Most severe lesions in right frontal lobe; multiple small foci bilaterally.
Case 2	66	M	Chronic lymphatic leukemia	3½ yr.	Left-sided homonymous hemianopsia; progressive left-sided hemiparesis; apathy & confusion.	6 mo.	Most severe involvement in right occipital lobe, but bilateral foci
Lloyd"& Urich[3] (1959)	57	F	Lymphosarcoma	8 mo.	Headaches; left-sided sensory impairment; impaired vision.	1 mo.	Multiple small lesions in cortex, subcortical gray matter & pons
Fisher et al.[8] (1961)	54	M	Carcinomatosis, multiple organs; primary source undetermined.	1½ yr.	(Chronic peripheral neuropathy); visual impairment; terminally, right-sided hemiplegia, with aphasia.	(1½ yr.) 5 mo.	Chronic peripheral neuropathy; widespread bilateral lesions, more extensive in left cerebral hemisphere; small foci in spinal cord.
Hallervorden & Hoelscher[9] (1961)	47	F	Sarcoidosis	2 yr.	Progressive unsteadiness of gait; impairment of vision.	4 mo.	Typical lesions & cell changes
Sibley & Weisberger[10] (1961)	57	M	Chronic lymphatic leukemia	6 yr.	Left-sided homonymous hemianopsia; progressive left-sided hemiparesis; hemihypesthesia.	7 wk.	Typical lesions & cell changes
Dolman & Cairns[11] (1961)	51	M	Hodgkin's disease	13 yr.	Dementia; dysarthria; left-sided homonymous hemianopsia; left-facial-muscle weakness, left-sided palatal weakness & left-sided ataxia; terminally; dysphagia, left-sided flaccid hemiparesis & right-sided spastic hemiparesis.	4½ mo.	Multiple small foci in frontal lobes & internal capsules; large destructive lesions in right parietal & left occipital lobes & cerebellar white matter; typical cell changes, including numerous giant astrocytes, some with mitoses.

*The case report contains no record of post-mortem findings other than those in the central nervous system.

Although the pre-existing disease was frequently of many years' duration, as indicated in Table 1, the neurologic illness was relatively brief. On an average it ran a course, from onset to death, of three to four months. Hallervorden's[4] first case, in which neurologic symptoms began one year before death, is exceptional.

TABLE 1 (*Concluded*).

SOURCE OF DATA	AGE	SEX	ASSOCIATED DISEASE		NEUROLOGIC DISORDER		OUTSTANDING NEUROPATHOLOGIC FEATURES
			DIAGNOSIS	DURATION	PRINCIPAL MANIFESTATIONS	DURATION	
	yr.						
Present report:							
Case 1[1]	71	F	Chronic lymphatic leukemia	16 yr.	Progressive left-sided hemiparesis; dementia; visual impairment, progressing to blindness; dysarthria.	4 mo.	Right occipital region most severely affected; early lesions in left occipital region; many giant astrocytes; some with mitoses.
Case 2[1]	73	F	Chronic lymphatic leukemia	5 yr.	Irritability & depression; headache; aphasia; right-sided hemiparesis; right-sided homonymous hemianopsia leading to blindness.	4 mo.	Widespread bilateral lesions, most extensive in left parieto-occipital region; many lesions in brain stem & cerebellar white matter; peculiar cell changes in cerebellar granular layer (cf. Cases 8 & 9).
Case 3[1]	42	M	Hodgkin's disease	10 mo.	Aphasia; right-sided hemiparesis.	2 mo.	Multiple small foci, most abundant in left parietal region; giant astrocytes rare.
Case 4	65	M	Chronic myelogenous leukemia	2½ yr.	Left-sided hemiparesis: dysarthria; emotional lability.	4 mo.	Rather sparse lesions bilaterally, but chiefly right frontoparietal; no giant astrocytes; plasma cells in lesions.
Case 5	49	M	Lymphosarcoma	2½ yr.	Right-sided hemiparesis; intellectual impairment; later, aphasia.	3 mo.	Multiple bilateral lesions; typical cell changes.
Case 6	31	M	Hodgkin's disease	7 yr.	Right-sided homonymous hemianopsia & hemiparesis; left-sided cerebellar ataxia; later, blindness.	7 mo.	Severe lesions bilaterally, most extensive posteriorly & in left cerebral hemisphere; left cerebellar white matter severely affected; right less so; no giant astrocytes.
Case 7	82	M	Coronary-artery disease; healed apical tuberculosis.	±15 yr.?	Mental slowness; dysarthria; minimal left-sided hemiparesis.	1 mo.	Scattered small lesions in cerebral hemispheres and brain stem; many giant astrocytes, 1 with mitosis.
Case 8	42	M	Chronic myelogenous leukemia	2 yr.	Vertigo, with falling to left; dementia; terminally, left-sided hemiparesis.	3 wk.	Widespread lesions, more extensive in right cerebral hemisphere; unusual lesions in granular layer of cerebellar cortex, with remarkable cell changes.
Case 9	68	F	Carcinomatosis (primary source, breast)	2 yr.	Vertigo; dysphagia, left-facial-muscle weakness; ataxia of right limbs; nystagmus.	2 mo.	Lesions most extensive in cerebellum & brain stem; few in cerebral hemispheres; peculiar changes in cerebellar cortex, as in Cases 2 & 8.
Case 10	35	M	Lymphosarcoma (lymphocytic lymphoma)	7 yr.	Progressive aphasia & right-sided hemiparesis; dysphagia; terminally, coma.	3½ mo.	Extensive lesions in both cerebral hemispheres, more on left; typical cell changes.

TABLE 2. *Pathologic States Associated with Progressive Multifocal Leukoencephalopathy.*

DISEASE	NO. OF CASES
Hodgkin's disease	6
Chronic lymphatic leukemia	4
Lymphosarcoma	3
Chronic myelogenous leukemia	2
Sarcoidosis	2
Carcinomatosis	2
Miliary tuberculosis	1
Coronary heart disease	1
Unknown (old age)	1
Total	22

In 4 cases the duration of the neurologic illness was one month or less. The onset was gradual or insidious, and the course relentlessly progressive in all cases in which the records are sufficiently complete on these aspects.

The neurologic symptoms and signs in most cases were those of a diffuse but asymmetrical disease of the cerebral hemispheres. Hemiparesis, spastic or flaccid, was frequent, occurring in 17 of the 22 cases (9 left and 8 right). Bilateral hemiparesis often occurred in the terminal phases of the illness, but was never an early sign. In the case reported by Dolman and Cairns[11] hemiparesis, eventually bilateral, was preceded by unilateral ataxia of the limbs and homolateral lower-cranial-nerve palsies. Some degree of mental change, consisting of impairment of awareness or orientation, decline in intellectual abilities and (in some cases) abnormal emotional responses, occurred sooner or later in nearly every case.

Vision was impaired in a large proportion of cases. Seven patients had generalized visual loss from the first, and 5 had a homonymous hemianopsia. Four of these 12 patients became totally blind, although the pupils continued to react to light. The changes in

vision may be ascribed in each case to lesions in the visual-projection fibers of the occipital lobes. Other ocular abnormalities were considerably less frequent. Paralysis of conjugate gaze to the paretic side in the presence of a hemiparesis was occasionally recorded (2 cases); nystagmus was mentioned in 2. The only clear isolated extraocular-muscle palsy was a lateral rectus weakness in Case 2. In the case presented by Fisher et al.[8] a transitory optic neuritis* preceding the generalized neurologic illness was associated with unilateral pallor of the optic disk, and in that of Bateman, Squires and Thannhauser[6] the left disk was described as atrophic. In all the other cases the optic disks either were stated to be normal or were not specifically mentioned; in none was there papilledema.

Thirteen patients had abnormalities of speech. In 7, the abnormality was an aphasia, generally with both expressive and receptive components, that could



FIGURE 1. *Low-Power Photomicrograph of the Cerebral Cortex and White Matter in Case 5, Showing Multiple Demyelinative Lesions of Varying Size (Loyez Method for Myelin, X3).*

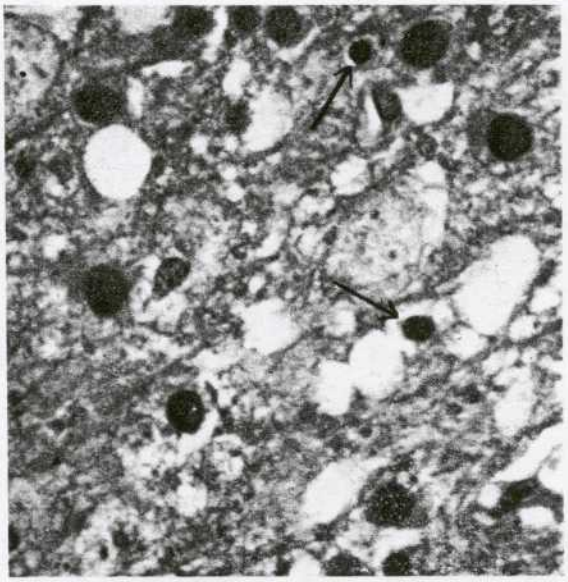


FIGURE 2. *Photomicrograph in Case 5, Showing Enlarged, Densely Basophilic Oligodendrocyte Nuclei with Loss of Nuclear Detail (Hematoxylin and Eosin Stain X450). Oligodendrocyte nuclei of normal size are shown by the arrows.*

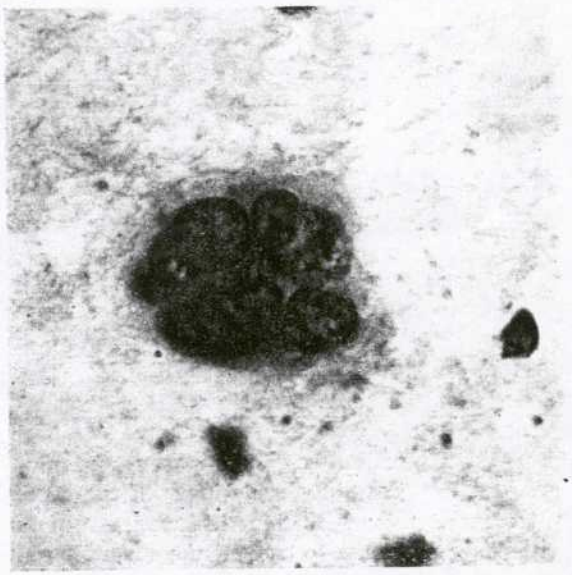


FIGURE 3. *Photomicrograph of a Giant Astrocyte with Multiple Hyperchromatic Nuclei in Case 1 (Hematoxylin and Eosin Stain X900).*

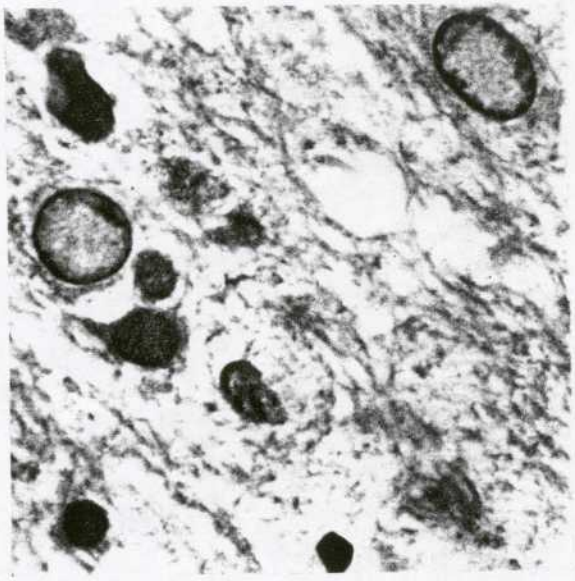


FIGURE 4. *Photomicrograph in Case 5, Showing Two Enlarged Oligodendrocyte Nuclei Containing Eosinophilic Inclusions (Hematoxylin and Eosin Stain X900). An oligodendrocyte nucleus of normal size is shown in the lower left corner.*

Thirteen patients had abnormalities of speech. In 7, the abnormality was an aphasia, generally with both expressive and receptive components, that could

*Post-mortem examination of the optic nerves showed no lesions.

be related to extensive lesions in the dominant (left) cerebral hemisphere. In the 6 others, it was a dysarthria.

Sensory impairment involving one side of the body was recorded in 4 cases. This was associated with a hemiparesis on the same side in 3. In the case of Lloyd and Urich[3] the only evidence of a unilateral disorder was "numbness down the left side of the body, with impaired sensation and diminished vibration sense below the left knee."

Impairment in swallowing (dysphagia) probably occurred in many of the patients as the end neared; it was specifically recorded, however, in only 4.

In 2 patients (Cases 8 and 9), the principal neurologic symptoms and signs were referable to lesions in the cerebellum and brain stem. These consisted of vertigo, a tendency to fall to one side (Case 8), nystagmus (Case 9), dysphagia (Case 9), unilateral ataxia (present also in Case 6) and, in Case 9, crossed signs (left-facial-muscle weakness, right-sided ataxia).

Unsteadiness of gait, not further specified, was recorded in 2 cases.[4,9] In a single case (Case 2 of Hallervorden[4]) there was a movement disorder of a type associated with basal-ganglion disease — that is, generalized choreiform movements.

Headaches were infrequent. They were mentioned as a prominent symptom in only 2 cases, and were either absent or minimal in the others. None of the patients had convulsive seizures.

Cerebrospinal-Fluid Findings

A consistent and significant feature of the entire group of cases was the minimal degree of abnormality in the cerebrospinal fluid. Thus, of the 11 cases* in which the cerebrospinal fluid was examined, the findings were entirely normal in 6. In 2, the only abnormality was a slight elevation of pressure (275 mm.[6] and 200 mm.[10]). A slight increase in cells was recorded in 2 — 25 lymphocytes per cubic millimeter (Case 1), and 6 "white blood cells" per cubic millimeter[11]; the cell count was normal, or not mentioned, in the others. In 2 cases there were minimal elevations of total protein: a "slight rise"[7] and 50 mg. per 100 ml.[11] respectively.

Electroencephalographic Findings

Electroencephalography was abnormal in every case in which it was done (7 of the 22). The reports were kindly reviewed by Dr. John A. Abbott, who summarized the findings as follows: "Diffuse slow-wave (delta or theta) activity of a sort in no way distinctive of this disorder, with normal activity persisting or obliterated and with asymmetries corresponding with the structural abnormalities. In 1 case (Case 1) flattening and sharp waves were noted on the side of greater structural abnormality."

Radiologic Findings

Plain films of the skull, whenever taken, invariably were normal. In all 3 cases in which pneumoencephalography was performed (Case 6 and those of Christensen and Fog[7] and Bateman et al.[8]) the findings excluded a space-occupying lesion. In the only case in which cerebral angiography was done this showed a normal vascular pattern.[10]

A localization study using a radioactive isotope (As^{74}) was done in only 1 case (Case 2), with normal findings.

Pathological Aspects

Although the lesions in the central nervous system were of the same character in all 22 cases, they varied considerably from case to case in location and extent. As a rule, they were most numerous in the cerebral hemispheres, but often the brain stem and cerebellum were severely affected. The spinal cord, when examined, was normal or at most showed minimal changes. In the previous publication[1] evidence was given for considering progressive multifocal leukoencephalopathy to be a distinct neuropathologic entity that cannot be classified with hitherto recognized diseases of the central nervous system. The combination of multiple demyelinative lesions of all possible gradations in size and stage of evolution (Fig. 1), with remarkable changes in oligodendrocytes (Fig. 2) and, often, in astrocytes (Fig. 3), does not occur in any other disease known to me. The appearance of the lesions suggests that progression of the clinical disorder results from the enlargement and confluence of small lesions and the continuous additions of new ones. The earlier description[1] placed considerable emphasis on the hyperplasia of astrocytes into bizarre giant forms, which resembled neoplastic cells. It is now apparent, however, that the astrocytes do not undergo this alteration in all cases. On the other hand, enlargement of oligodendrocyte nuclei, with dense basophilia and loss of nuclear detail, is invariably present. Eosinophilic intranuclear inclusions have been seen within these abnormal oligodendrocytes in nearly every case (Fig. 4), but may not always be found (for example, in Case 4, and in the case of Dolman and Cairns[11]). Experience with the additional cases here reported has suggested still another form of cellular hypertrophy unknown to us from previous experience. In Cases 2, 8 and 9 there were, in lesions in the granule-cell layer of the cerebellar cortex, large nuclei, which, from their form, location and arrangement, have been tentatively identified as altered cerebellar granule neurons (Fig. 5). Although the identity of these cells has not been established beyond all doubt, this cell change seems

*The case of Fisher et al.[5] (who kindly allowed me to see their unpublished manuscript) is not included. In this, the protein was elevated (435 mg. per 100 ml.) on a single examination done while the patient was under observation for chronic peripheral neuropathy, before evidence of cerebral disease had appeared.

to be of sufficient interest to warrant a preliminary note.



FIGURE 5. *Photomicrograph of the Cerebellar Cortex in Case 8, Showing Unusual Nuclei in the Granular Layer (Hematoxylin and Eosin Stain X250).*

Near the top, just beneath the sparsely cellular molecular layer, are normal granule neurons. Below these, similarly grouped into clusters, are larger nuclei belonging to cells that may be pathologically enlarged granule neurons.

The earlier impression that the lesions have a predominantly perivascular distribution[1] has not been borne out by the present studies. Examination of serial sections generally discloses at least one minute vessel within even small lesions, but in view of the large numbers of such vessels normally present in the brain, it cannot be stated that this relation is a significant one. This conclusion is in agreement with the findings of Fisher et al.[8] On the other hand, the additional case material does confirm the previous finding that inflammation, in the form of perivascular lymphocytic infiltrations, is, with rare exceptions, minimal or absent.

The pathologic changes in organs other than the central nervous system were in each case typical of the particular disease present. There was no evidence that the cases of chronic disease associated with progressive multifocal leukoencephalopathy differed from others of the same disease in which this neurologic disorder was present. Although in most cases the underlying disease was such that in itself it would have been expected ultimately to have been fatal, many of the patients apparently died as a result of the devastating effects of the lesions in the brain. It seems reasonable to suppose that if the cerebral disease could have been prevented or effectively treated, many of the patients would have survived longer than they did.

Etiologic Considerations

The cause and pathogenesis of progressive multifocal leukoencephalopathy remain unknown. However, it occurs with conditions in which immunologic hyporeactivity has been demonstrated (lymphomas,[12-14] leukemia,[13] sarcoidosis,[15,16] carcinomatosis[17,18] and old age[19]), and therefore decreased resistance to infections might be expected. The changes in oligodendrocytic and astrocytic nuclei described above are consistent with the cytopathologic effects of a virus, which, in the presence of impaired immunologic responses, could result in atypical lesions. It is hoped that in the future cases of this sort will be recognized so that appropriate investigations may be undertaken during life and studies carried out on fresh tissues obtained at autopsy.

Summary and Conclusions

Ten cases of progressive multifocal leukoencephalopathy, an unusual central-nervous-system disease with distinctive neuropathologic features occurring late in the course of several forms of chronic illness, are presented. To these are added 12 cases studied by others, giving a total of 22.

The outstanding clinical features of this condition are those of a rapidly progressive focal or asymmetric disorder of the brain unaccompanied by increased intracranial pressure or significant cerebrospinal-fluid changes. It has most frequently been associated with malignant lymphoma or leukemia, but may occur with sarcoidosis, carcinomatosis, miliary tuberculosis or, rarely, advanced age without neoplastic or granulomatous disease.

Evidence is cited that the one factor common to all the chronic diseases met with in this series is the presence of relative immunologic unresponsiveness. The cause of progressive multifocal leukoencephalopathy remains unknown, but the suggestion is made

that the nervous-system lesions are consistent with an atypical form of virus infection.

Further progress in understanding this condition will depend upon the study of cases during life, and of fresh tissue samples. For these purposes, recognition of cases during life, which should now be possible, is urged.

Two additional cases, both associated with long standing chronic lymphatic leukemia, have kindly been brought to my attention and I have been permitted to examine neuropathological sections from both. The first, from Dr. Elliott L. Mancall, Department of Neurology, Jefferson Medical College, Philadelphia, Pennsylvania, and to be reported by him, is that of a forty-one-year-old man in whom the only neurologic abnormality consisted of generalized convulsions five days before death. The second, from Dr. C. L. Dolman, Department of Pathology, Vancouver General Hospital, Vancouver, B. C., occurred in a fifty-eight-year-old man with a very brief terminal neurologic illness who had had generalized convulsive seizures for four years, referable to an oligodendroglioma discovered post mortem as an incidental finding.

Drs. Raymond D. Adams, Benjamin Castleman, Charles S. Kubik, Byron H. Waksman and Barry Arnason, of the Massachusetts General Hospital, Professor Julius Hallervorden, Max-Planck-Institut für Hirnforschung, Giessen, Western Germany, and Dr. John F. Enders have given me friendly help and encouragement, for which I am indeed grateful. I am greatly indebted to Dr. Waksman for immunologic advice and for suggesting how viral infection could account for the neuropathologic lesions in this series of cases.

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CHLORPROPAMIDE IN PATIENTS ON HIGH INSULIN DOSAGE*

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A RECENT review of patients from the Diabetes Clinic of the Boston City Hospital revealed a substantial number doing well on chlorpropamide¶ whose insulin requirement had exceeded 50 units. Because it has become almost axiomatic that these patients should not be expected to do well on the sulfonylurea type of agent, the subject was pursued further. Additional patients receiving 50 units of insulin or more a day were transferred to chlorpropamide, and their response tabulated. The results in 28 patients constitute the basis of this report.

Methods and Materials

Criteria for inclusion in the study were as follows: the diabetes was of the maturity-onset type and required 50 units of insulin or more per day at the time of transfer to chlorpropamide; patients with a history of diabetic acidosis were excluded (carbon dioxide below 15 milliequiv. per liter); and all patients must have been maintained on chlorpropamide long enough to make a clear evaluation of control. If a good response was obtained a placebo trial was given in accordance with the single-blind design of the study, as outlined below. The charts of all patients receiving chlorpropamide before June, 1960, were examined, and all those fulfilling the criteria stated above were included. In addition, all patients seen in the clinic between July, 1959, and June,

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¶Kindly supplied as Diabinese by Charles Pfizer and Company, Incorporated, Brooklyn, New York.