Progressive multifocal leukoencephalopathy. A hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin’s disease by Karl-Erik Åström, Elliot L. Mancall and Edward P. Richardson Jr (From the Departments of Neurology-Neuropathology, Harvard Medical School, and the Neurology Service and the Neuropathology Laboratory, Department of Pathology, Massachusetts General Hospital, Boston.) Brain 1958; 81: 93–111, plates VII–XIV.

Although the most cited paper describing progressive multifocal leukoencephalopathy is that published by E. P. Richardson based on 22 cases (N Engl J Med 1961; 265: 815–823), these notifications from colleagues throughout the world were triggered by the 1958 Brain paper. As E. P. Richardson wrote in the monograph ‘The Remote Effects of Cancer on the Nervous System’, edited by Lord Brain and Forbes Norris (1964), ‘some years ago in the course of the regular post-mortem examination of the brains of patients coming to autopsy at the Massachusetts General Hospital, we encountered two cases of a remarkable disorder of the cerebral white matter that was unlike anything we had seen before’. After reviewing the direct effects of leukaemia and Hodgkin’s disease on the nervous system, Åström and colleagues described the clinical and pathological features of three cases. A 71-year-old seamstress presented with progressive left hemiplegia followed by right hemiparesis, cortical blindness, bulbar failure and coma. A 73-year-old accountant presented with right hemiparesis, homonymous hemianopia and left angular gyrus syndrome, followed by focal brainstem involvement, blindness and coma. Each had chronic lymphatic leukaemia. A 42-year-old male executive with Hodgkin’s disease presented with generalized weakness, right hemiparesis, confusion,aphasia and coma. Each died within 4 months of the neurological presentation. (Generously, in 1958, we allocated eight full text pages and eight further full pages of plates to the case reports alone.) Pathologically, each case showed widely disseminated small perivascular foci of myelin sheath destruction, with relative sparing of axis cylinders. All parts of the nervous system were involved, although the spinal cords were not examined. An evolving pattern of lesions could be observed suggesting progressive stages in development of the pathological process—from collections of pleomorphic microglia with intact myelin, to areas of extensive and confluent demyelination, microglial activation, astrocytosis and some neuronal loss with ‘senile plaques’ and Alzheimer neurofibrillary changes. Special attention was drawn to cells with basophilic staining nuclei and a surrounding cytoplasmic halo. The evidence suggested that these were oligodendrocytes. Later, giant cells with hyperchromatic nuclei considered to be reactive astrocytes, some undergoing mitosis and mimicking neoplastic cells, made their appearance. Systematically, the authors considered but rejected classification of these three cases as one or other of the demyelinating diseases recognized at the time. Nothing seemed to fit. But there were similarities to five cases described in the 1930s and 1940s. Through his contacts with neuropathologists worldwide, it proved possible for E. P. Richardson to review archival material from three of these historical cases (two with Hodgkin’s diseases and one with sarcoidosis). Each clearly had the same disease as those now being described in the 1958 Brain paper. For the future, Åström and colleagues considered that the combination of rapidly progressive dementia, pyramidal involvement and blindness, often with brainstem features indicating involvement of the posterior cerebral hemispheres, might suggest their newly described demyelinating disorder associated with morphologically abnormal oligodendrocytes. This was evidently a rare complication, having affected only three of 234 cases of leukaemia or lymphoma subjected to neuropathological examination between 1937 and 1956. Of aetiology they knew nothing, and no hypothesis was offered. The viral nature of this disorder complicating immune suppression, and the identification of JC virus as the causative organism, lay ahead; but the clinical and pathological foundations for a new disease of the CNS was now in place.

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