Penetration of Neuronal Perikarya by Capillaries in Chronic Limbic Encephalitis

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Abstract. In a case of chronic limbic encephalitis in a 57-year-old man many neurons in the pyramidal cell layer of the hippocampus bilaterally were penetrated by ingrowing capillaries. All gradations from slight to moderate indentation of the cell membranes to complete incorporation of the capillaries in the neuronal perikarya were observed. The penetrating capillaries retained their basement membranes. Because of the chronic inflammation there was extensive fibrous gliosis in Ammon’s horn. This apparently had an immobilizing effect on these neurons; it is postulated that proliferating capillaries of the active inflammatory process were unable to displace local neurons and instead grew against and through their perikarya.

Key Words: Capillary; Limbic encephalitis, chronic; Neurons.

INTRODUCTION

The nature of spatial relationships between nerve cells and capillaries varies from one part of the central nervous system to the other. In many areas capillary basement membranes are tightly surrounded by footplates of adjacent astrocytes that form a perivascular glial membrane, which as a rule, interposes itself between the vascular wall and neighboring neuropil. Elsewhere capillaries are more closely situated to nerve cells. In two areas containing neurons known to be involved in neurosecretory activity, the supraoptic and the paraventricular nuclei of the hypothalamus, such a close spatial relationship is particularly pronounced. Within these nuclei capillaries seemingly press themselves into the adjacent cytoplasm of neurons, as a part of the normal microscopic anatomy of these areas (1–3).

We describe a case where an unusually close and intimate spatial relationship between capillaries and neurons developed apparently as an acquired phenomenon. The patient had a chronic encephalitis centered on Ammon’s horns. Capillaries proliferated as part of the inflammatory reaction in an area where neurons seemed to be “tethered” and thus immobilized in their respective locations by dense fibrillary gliosis, which was itself a result of chronic inflammation in the area. It is possible that these neurons could not be displaced by proliferating capillaries, consequently the vessels indented the cell membranes of some neurons and deeply penetrated others. This speculation is offered only as a tentative explanation for this unusual phenomenon. Future observations of this type by us or by others may offer a more clear-cut cause-and-effect relationship between chronic gliotic encephalitis and the penetration of neurons by capillaries.

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CAPILLARIES IN NEURONS

REPORT OF CASE

This patient, a 57-year-old man with a history of a seizure disorder was found limp and unresponsive near the front door of his house. An ambulance was called and the paramedics found the patient to be in asystole. A cutaneous pacemaker was employed but blood pressure could not be obtained. The patient was a truck driver with a smoking history of one package daily for 40 years; he quit two years before death. Past medical history was significant in that he started having seizures two years before the terminal event: these seizures were both of the absence and grand mal types. He also had signs and symptoms of dementia which improved somewhat after anticonvulsant therapy (phenytoin 300 mg per day and myoline, dosage unknown) was instituted. Multiple cranial computed tomographic (CT) scans were normal, however magnetic resonance image (MRI) scanning showed a possible increased density in the right temporal lobe. The electroencephalogram (EEG) also revealed an abnormality in the same area. The patient continued to have approximately three seizures per week despite anticonvulsant therapy. On arrival to the emergency room he was in asystole and unresponsive. Further resuscitative efforts were unsuccessful and he was pronounced dead.

The general autopsy showed moderate to severe atherosclerosis of the abdominal aorta and the common iliac arteries and a 90% atherosclerotic occlusion of the circumflex branch of the left coronary artery with a recent myocardial infarct involving the lateral-posterior wall of the left ventricle. This recent infarct was considered the immediate cause of death. The rectum contained a villonodular polyp, but no frankly malignant change was encountered in it and all other examined organs were also free of neoplastic changes.

Neuropathological Findings: The brain weighed 1,350 grams and showed slight overall swelling with a moderate degree of bilateral tonsillar and uncal herniation. There was no atherosclerotic involvement of the cerebral arteries. External examination as well as multiple sections of the brain showed no visible alterations.

On microscopic examination mild chronic meningitis with focal infiltrates of lymphocytes and plasma cells was found over the frontal, parietal, temporal and occipital lobes of the brain. The parenchyma of these lobes was free of inflammation or other abnormalities except for the hippocampus on both sides which showed marked chronic inflammation with perivascular lymphocytic cells (Fig. 1), microglial nodules, neuronal cell loss (Fig. 2), and marked fibrillary gliosis (Fig. 3A) throughout.

With the Holzer stain (Fig. 3B) and with the immunoperoxidase technique for glial fibrillary acidic protein (GFAP) astrocytic processes were seen to surround the perikarya of nerve cells (Fig. 3C), particularly in the pyramidal cell layer. There was capillary proliferation seen as part of the active inflammatory process and in some areas the capillaries were impinging on the cell membranes of nerve cells deeply indenting them and causing marked deformities in the outlines of the nerve cells (Fig. 3D, E). In some neurons deep penetration could be observed (Fig. 3F) while in others the capillaries were completely surrounded by nerve cell cytoplasm (Fig. 3G). In occasional intraneuronal capillaries red blood cells were also observed (Fig. 3H). In some nerve cells the capillaries was evident in cross-section (Fig. 3I) With Wilder's reticulin stain longitudinal and cross sections demonstrated that the capillaries maintained their basement membranes even within the neuron (Fig. 3J, K). Their endothelial cells stained positively for Ulex europeus lectin (Fig. 3L).

No viral inclusion bodies were identified in neuronal or glial cells. Immunoperoxidase staining for Herpes simplex virus antigen were negative in paraffin-embedded sections and electron microscopic (EM) studies of the inflamed areas revealed no viral particles.

Attempts were made to examine the ultrastructural appearance of the interface between capillary walls and surrounding cytoplasm of the neuronal perikarya. As is often the case with formalin-fixed autopsy material where the need for EM examination was not anticipated at the time of the autopsy, the preservation of tissues was not optimal. However, capillaries could be recognized by their endothelial cells and the red blood cells in their lumina. The cytoplasm of nerve cells displayed many clumps of adult-type lipofuscin in addition to ribosomes, mitochondria and bundles of neurofilaments (Fig. 4). Granular basement membrane material with interspersed collagen fibers was well recognized next to endothelial cell cyto-

Fig. 1. Ammon's horn: A small vein is surrounded by lymphocytic infiltrate. Hematoxylin and eosin (H&E). ×100.

Fig. 2. Endplate of hippocampal pyramidal neurons: microglial proliferation, neuronal loss and increased fibrous astrocytes. H&E. ×240.

Fig. 3. A. Overview of left hippocampus: Marked fibrous gliosis in atrophic Ammon's horn. Holzer stain. ×6. B. Glial fibrils surround surviving neurons. Holzer stain. ×220. C. Fibrous astrocytes next to nerve cells surround the latter with their processes and appear to
Fig. 4. A capillary (center) containing a red blood cell is seen against the cell wall of a nerve cell (to the right and above the capillary basement membrane). The neuronal cytoplasm contains mitochondria, ribosomes, neurofilaments and clumps of lipofuscin. × 7,500.

Fig. 5. Interface between penetrating capillary and neuron: endothelial cytoplasam seen on the left side; the capillary basement membrane contains some fragments of collagen fibers. The neuronal cytoplasm (to the right and on top) has mitochondria and filaments with focal condensations attached to the neuronal side of the capillary basement membrane. In some areas (arrows) a thin membrane separates the ribosomes from the capillary basement membrane, but in others (double arrows) no such interposed membrane can be seen. × 30,000.
plasm. On the neuronal side fragments of neurofilaments with focal condensations and ribonucleic acid granules were separated from the capillary basement membrane in some areas (Fig. 5, arrow) but such a membrane was not discernible in other areas (double arrow). We could not state with certainty whether part of the neuronal cell membrane was eroded in vivo or fragmented because of suboptimal fixation, the latter perhaps more likely. The electron micrographs, however, left no doubt about the fact that no astrocytic cell processes, not even in compressed or rudimentary form, were interposed between capillary walls and the surrounding neuronal perikarya.

**DISCUSSION**

It appears that our patient suffered from a chronic form of limbic encephalitis centered on the hippocampus bilaterally. The rest of the brain showed only moderate lymphocytic meningitis, but no parenchymatous involvement. There was no loss of cerebellar Purkinje cells and signs of brain stem encephalitis were also absent. Limbic encephalitis most commonly complicates a malignant neoplasm of extraneural tissue (most often, but not exclusively, a small cell anaplastic carcinoma of the lung). In our case the only neoplasm found at autopsy was a villo-adernomatous polyp in the rectum, a lesion that may be considered as precancerous but it did not show histologic evidence of malignancy. Limbic encephalitis however may occasionally be found in patients who do not harbor a detectable malignancy (4, 5) and we believe that our case probably belongs in that category. The chronic inflammation was accompanied by active capillary proliferation. Growing capillaries as a rule have no difficulty finding space to accommodate their proliferation since the soft brain substance will yield to the newly sprouting vascular branches. We may postulate, although certainly not prove, that in the present case the chronic inflammatory process made such spatial compliance more difficult: surviving neurons in the area were possibly trapped and immobilized by dense fibrous gliosis and could not be displaced by the growing capillaries. As a result of these changes their perikarya became indented and penetrated by the small vessels. Unlike the close neuronal-capillary relationship in neurosecretory centers of the hypothalamus where such spatial arrangement appears to have a physiological purpose related to secretory activity, in the present case we were observing an acquired alteration with no apparent physiological connotations. On the other hand, it appears that penetration of neurons did not have a harmful effect on the capillaries themselves: their lumina remained patent, their lining endothelium and basement membranes structurally intact. Also, the affected nerve cells did not show visible damage to their cytoplasm or nuclei, other than a change in the configuration of the cells as a whole, as a result of indentation or penetration by the capillaries. Therefore, it is probable that neurons did not suffer serious functional damage either, from this unusual alteration. Although in the areas of neuronal penetration astrocytic footplates were absent from around the capillaries, this fact did not seem to lead to gross or microscopic edema in the involved areas. Compared to the total vascular bed of the region, the number of capillaries making intimate contact with neurons without interposed astrocytic processes was very small and would not be expected to alter whatever role astrocytes have in maintaining the blood–brain barrier in a given area of the brain.

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**REFERENCES**


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