Neuronal heterotopia with capillary penetration of neurons and cortical dysplasia in a patient with complex partial seizures

Case report

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Unusual pathological findings were encountered in a temporal lobectomy specimen from a 9-year-old boy with intractable complex partial seizures. Magnetic resonance imaging revealed an enlarged left temporal lobe, with diffuse high signal intensity over the cortex and poor gray-white differentiation on T2-weighted imaging; single-photon emission computerized tomography showed decreased blood flow. Active epileptiform discharges were identified in the left temporal lobe with focal slow waves and generalized epileptiform paroxysms. Pathologically, the cortex revealed changes of focal cortical dysplasia with extensive disorganization of neuronal morphology, layering, and orientation as well as focal polymicrogyria. The cortical-white matter junction was indistinct with extensive neuronal heterotopias in the white matter. Large pale balloon cells akin to those seen in tuberous sclerosis were found scattered within the cortex and white matter. The most striking finding was that of a heterotopic nodule in the white matter, which revealed abnormal neurons with penetration of cell bodies by capillaries. Ultrastructurally, there were no degenerative changes in these neurons, and this unusual phenomenon is attributed to a developmental disturbance affecting neuronal, glial, and vascular elements.

KEY WORDS • temporal lobe • epilepsy • ultrastructural study • capillary • neuron

In 1990, Kepes, et al., described the unusual finding of penetration of neurons by capillaries in the hippocampus of a 57-year-old man with a history of a seizure disorder. Based on the finding of chronic lymphocytic infiltrates and gliosis in the hippocampus, the authors postulated that this phenomenon was a sequel to the inflammation and scarring that immobilized the neurons, thus causing proliferating capillaries to grow through their perikarya. We describe capillary penetration of neurons in a temporal lobectomy specimen in a 9-year-old patient with complex partial seizures. The pathological findings indicate that, in the present case, this curious phenomenon is attributable to a developmental disturbance affecting neuronal and vascular elements.

Case Report

This 9-year-old boy was admitted to The Hospital for Sick Children with intractable seizures. He had a long-standing history of complex partial seizures with an epigastric aura and secondary generalized tonic clonic seizures since the age of 3 years. He exhibited behavioral problems and learning difficulties in school. He had been treated with carbamazepine, primidone, valproic acid, and clonazepam.

Examination. Neurological examination was unremarkable. Computerized tomography (CT) with and without contrast enhancement showed no abnormal findings. On magnetic resonance (MR) imaging, a slightly enlarged left temporal lobe was seen on coronal cuts. Diffuse high signal intensity over the cortical region as well as poor differentiation of gray and white matter was shown on T2-weighted imaging in the same area, involving the mesial temporal region. Interictal single-photon emission CT (SPECT) using 99mTc-hexamethylpropyleneamine demonstrated decreased regional cerebral blood flow over the left temporal and occipital regions.
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Electroencephalographic (EEG) tracings showed active epileptiform discharges in the left temporal area with focal slow waves over the same region and generalized epileptiform paroxysms. Prolonged closed-circuit video EEG telemetry obtained with sphenoidal electrodes revealed focal onset of typical complex partial seizures in the left temporal area, including the inferior mesial temporal region, during the ictal events. An amobarbital injection test was performed in the internal carotid artery, but the dominant hemisphere for language was not confirmed.

Operation. A left frontotemporal craniotomy was performed under neuroleptic anesthesia. Pre-excisional electrocorticography (ECoG) showed a very active epileptiform disturbance in the middle portion of the middle temporal gyrus as well as anterior portions of the inferior and superior temporal gyri. A single depth electrode directed to the hippocampus revealed mild active epileptiform disturbance at the deepest contacts synchronous with the surface epileptogenic discharges. Following left anterior temporal lobectomy as well as hippocampectomy, under cortical stimulation for identification of the speech area, postexcisional ECoG showed some residual epileptiform activity in the middle temporal gyrus, in addition to diffuse epileptiform activity suggestive of generalized discharges.

Pathological Preparation. The temporal lobectomy specimen was submitted in toto for conventional histological, Golgi impregnation (for delineation of dendritic morphology), and electron microscopic preparation. The following stains were performed on histological sections: Bielschowsky, Nissl, hematoxylin and eosin, and Luxol fast blue. Immunostaining for the following antibodies was performed by the peroxidase-antiperoxidase/avidin-biotin complex methods: glial fibrillary acidic protein (GFAP), polyclonal 1:200; factor VIII, polyclonal 1:50; synaptophysin; monoclonal phosphorylated neurofilaments, 1:25; and neuron-specific enolase, polyclonal 1:250.

For electron microscopy, tissue was fixed in the universal fixative (equal parts of 4% formaldehyde and 1% glutaraldehyde), postfixed in 1% OsO4, and embedded in Epon. Semithin sections were stained with uranyl acetate and examined under a Philips 201 transmission electron microscope. Tissue was also processed by the modified rapid Golgi technique (as outlined elsewhere), which selectively impregnates dendrites with osmium dichromate of about 10% neurons, thus allowing for clear visualization of individual neurons and their dendritic arborization patterns. Following Golgi impregnation, the tissue was prepared in a paraffin block and sections were obtained at 50-μm intervals.

Pathological Findings. The first specimen represented the temporal lobe measuring 6 x 3.5 x 1.4 cm. On gross examination an abnormal gyral pattern was present in a 4.2 x 3-cm area over the cortical surface, this area having a paucity of sulci with broad superficial gyri. In many areas, the gray-white matter junction was ill defined and, in the deep white matter, a grayish white ill-defined nodularity was apparent. The second specimen represented the hippocampus and medial temporal lobe structures measuring 2.2 x 1.5 x 1.5 cm. The remainder represented material obtained by the Cavtron ultrasonic aspirator, up to 15 ml in total.

Extensive cortical abnormalities were seen in multiple microscopic sections, with shallow and indistinct sulci and focal polymicrogyria. There was extensive disorganization of neuronal layering, with clusters of maloriented neurons. A scattering of abnormal neurons and large cells with eosinophilic pale glassy cytoplasm with eccentric nuclei ("balloon cells") was seen throughout the cortex. The latter cells were somewhat reminiscent of cells seen in cortical tubers. Clusters of reactive astrocytes were encountered throughout the cortex, often in association with abnormal neurons or balloon cells.

Several notable abnormalities were encountered in the white matter. The first represented heterotopias. The cortex-white matter junction was often indistinct with spilling of heterotopic gray matter into the subcortical white matter. There were extensive white matter heterotopias consisting of small and large neurons and oligodendrocytes as well as scattered reactive astrocytes. The heterotopic masses were often confluent, replacing a sizable proportion of white matter. The second notable finding was the occurrence of clusters of pale balloon cells and reactive astrocytes with decreased myelin in these foci as indicated by the Luxol fast blue stain. These were also associated with heterotopic neurons and collections of anomalously oriented distorted neuritic processes in the white matter, demonstrated by the Bielschowsky and neurofilament stains. The balloon cells were nonreactive for GFAP, but some stained for neuron-specific enolase and neurofilament. The heterotopic neurons revealed punctate synaptophysin positivity on the surface.

The third and most striking finding in the white matter was a nodular lesion, composed of giant aberrant neurons (Fig. 1), intermixed with coarse neurites and neuropil and scattered reactive astrocytes. A few pale balloon cells were also part of this lesion. These neurons exhibited extensive abnormalities of Nissl substance and irregular sizes and shapes, and contained neurofilamentous material (Fig. 2). Binucleate neurons were also found. There was a proliferation of capillaries throughout this nodule, with the notable feature being penetration of the neuronal soma by the capillaries (Fig. 1). There were no degenerative changes in the neurons penetrated by capillaries, nor was there evidence of extensive scarring or gliosis. There was no evidence of an inflammatory process.

Mild reactive gliosis was identified in the CA4 region of the hippocampus. Golgi impregnations revealed abnormal arborization and orientation of dendrites in the neurons in the cortex and the subcortical neuronal heterotopias.

On electron microscopy, the large neurons possessed large nuclei with dispersed chromatin and prominent nucleoli and abundant cytoplasm with disorganized collections of Nissl substance represented by perinuclear polyribosomes. The cytoplasm contained abundant microtubules and neurofilaments as well as mitochondria. Notable within the cytoplasm were capillaries
(Fig. 3) extending via invaginations. Some appeared to be entirely intraneuronal. All intraneuronal capillaries were invested by an intact basement membrane surrounding the endothelium (Fig. 3 right). There were no astrocytic processes interposed between the capillary basement membrane and the neuronal soma (Fig. 3 right). Neurons containing capillaries were similar in appearance to those without vascular penetration, and both were surrounded by neuropil with numerous synapses. Notably, there was no evidence of reactive gliosis or scarring surrounding the neurons with capillaries.

Discussion

In their report of autopsy findings in a 57-year-old man with chronic seizure disorder, Kepes, et al., described unusual pathology in the temporal lobes. The patient, who was found unresponsive, apparently suffered from absence and grand mal seizures 2 years prior to death, and had developed dementia. Autopsy examination revealed no evidence of a systemic malignancy. Based on the findings of perivascular lymphocytic infiltrates, microglial nodules, and gliosis in the hippocampus, as well as scattered lymphocytes and plasma cells in the meninges, a diagnosis of chronic limbic encephalitis was made. The patient did not have any other manifestations of a paraneoplastic encephalomyelitis or cerebellar degeneration. The pyramidal layer of the hippocampus of this patient was notable for capillary proliferation with neuronal penetration similar to the pathology encountered in our patient.

Kepes, et al., speculated that the observed phenomenon of capillary penetration was secondary to the inflammatory reaction. They postulated that surviving neurons became trapped and immobilized by dense fibrous gliosis and could not be displaced by growing capillaries, as a result of which their perikarya became indented and penetrated by the vessels. In our patient, there is evidence of a generalized dysgenetic process with cortical dysplasia, extensive white matter heterotopias, as well as collections of aberrant neurons and a scattering of pale, distended balloon cells akin to those seen in tuberous sclerosis, all of which have been described in epilepsy resections for cortical dysplasia. In our patient, the heterotopic nodule with neuronal capillary penetration was located in the deep temporal white matter, and the hippocampal neurons were not involved by this phenomenon. While the dysplastic cortex and white matter heterotopias and the CA4 region revealed scattered reactive astrocytes, there was no indication of dense gliosis or inflammation, and the neurons that were penetrated by capillaries contained an abundance of Nissl substance, as well as other or-

![Fig. 1](image1.jpg)

**FIG. 1.** Left: Low-power photomicrograph showing a heterotopic nodule (N) in the white matter (W). Luxol fast blue/H & E, x 22. Right: High-power photomicrograph showing large abnormal neurons within this nodule with penetration of cytoplasm by capillaries (arrow). Luxol fast blue/H & E, x 140.

![Fig. 2](image2.jpg)

**FIG. 2.** Photomicrograph showing accumulation of neurofilamentous material in the neurons, demonstrated by the Bielschowsky stain and immunostaining for neurofilament (inset, straight arrow). The unstained clefts represent capillaries penetrating the cytoplasm (curved arrow) x 140.
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Fig. 3. Electron micrographs of the nodule. Left: Section showing a neuron with penetration of the soma by a capillary (arrow). The neuronal cytoplasm contains abundant Nissl substance, most marked in the perinuclear region, as well as microtubules, neurofilaments, and mitochondria. N = Nissl; R = red blood cell inside the capillary lumen. X 1785. Right: Section showing an intraneuronal capillary with intact basement membrane (arrow) surrounded by neuronal cytoplasm containing neurofilaments (NF) and mitochondria (M). X 2250.

ganels and cytoskeletal components with no accumulation of lipofuscin or other degenerative changes. Thus the cortical and white matter lesions appear to be consequent to a primary developmental aberration and not acquired in nature. An intimate spatial relationship between neurons and capillaries is well recognized in the human suprachiasmatic and paraventricular nuclei, especially the former.2,3 Even "intraneuronal" capillaries have been described.7 While this relationship is a normal anatomical feature of these hypothalamic nuclei, we speculate that, in our temporal lobe lesion, the aberrant neurons developed an unusually intimate relationship to the cerebral vasculature as part of a developmental disregulation.

In the present case, there was significant correlation between the MR image,2 the EEG findings, and the pathology. The MR image revealed an expanded left temporal lobe with poor gray-white delineation and diffuse high signal intensity on T1-weighted imaging in the cortex; this correlates with the region of cortical dysplasia and the extensive heterotopias often blurring the deep cortical-white matter junction. The SPECT scan demonstrated decreased regional blood flow over the temporal and occipital regions of this hemisphere. Whereas the interictal and ictal EEG and pre-excitisional ECoG revealed active epileptiform disturbance, this focal epileptiform activity disappeared on the EEG tracings 2 years following anterior temporal lobectomy and hippocampectomy. Two years postsurgery, the patient is seizure-free on medication.

Our patient adds to the varied spectrum of pathology encountered in cortical and temporal lobe resections in children with epilepsy. The developmental disregulation in this case involved not only neurons and glial cells, but also cells of uncertain origin, notably the balloon cells (some of which possessed the immunophenotypic features of neurons), as well as cerebrovascular endothelium.

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References


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