HETEROTOPIC CEREBRAL GRAY MATTER AS AN EPILEPTOGENIC FOCUS

DONALD D. LAYTON, M.D.

(Chicago, Illinois)

Massive anomalies of fetal development often include heterotopias of gray matter in the brain. The combined defects in such cases are usually incompatible with life, and functional correlations are not possible. That heterotopias of cerebral gray matter may be related to symptoms in living people is of some clinical interest. This report is offered to illustrate the pathologic findings and clinical correlation of such a case. Reference will be made to some previous pertinent reports.

CASE REPORT

History: The patient was a white male, 43 years old at the time of his death. He weighed 4 pounds 12 ounces at birth, but his past medical history was essentially negative until the age of 9 years when he began to have recurrent right ear infections. He had scarlet fever at the age of 10 years with no recognized complications.

The seizure disorder began at 14 years of age. These early attacks were characterized by uncontrolled, inappropriate laughter, followed by unconsciousness. At first they occurred only every 3 months, but the frequency increased and he began having grand mal attacks as well. The attacks were sometimes preceded by an aura of “brightness”. He left high school in the second year, but the reason for this was not recorded. At 18 years of age he had 23 convulsions in one 48 hour period, and only then was anticonvulsive therapy instituted.

With anticonvulsant medication, the patient had no major seizures, but minor seizures occurred as often as 4 in one day or as infrequently as once in several months. The minor seizures were of the psychomotor clinical type, with automatisms. Some examples of his actions were that he might walk across the street with no memory of it, or might light a cigarette during an attack without knowing it.

During the interval in which his major seizures were controlled, he lost many jobs because of the minor ones. At one time he was employed to “feed” a blueprint machine. A psychomotor attack occurred while he talked with his employer. The patient was amnestic for the conversation in which he said he did not feel well and wanted to go home. His employment record included a variety of unskilled labors. For a time he worked with a municipal street crew, and his last job was as a watchman in 1957.

He was cared for in the clinics of the Research and Educational Hospitals of the University of Illinois from 1955 until 11 months before his death. An electroencephalogram in 1955 showed a spike focus in the right midtemporal lead, spreading negatively to the occipital leads. There were independent spike foci shown in the right midtemporal and anterior temporal leads with some slowing. The neurologic examination was said to be negative. Several entries in his chart gave evidence of his interseizure personality. They included these comments: “Takes medicine irregularly”, “Paranoid”, “Protest complaints”, “Question of operation”. Unfortunately there is no discussion in the chart as to whether the question of operation arose only in the mind of the resident who wrote it down or whether the patient had raised the question.

Neurosurgical intervention is considered at this institution in poorly controllable epileptics when the electroencephalographic abnormality is focal and especially when the clinical seizure type is psychomotor. Such an exploration in this case would have established an etiologic diagnosis but most probably would not have resulted in benefit to the patient.

*From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, Chicago, Illinois.
One month before his death he was admitted to another hospital for lethargy, depression, anorexia, and was seen by internists and psychiatrists but was discharged a few days before his death. His family said that he had refused to eat or to take his anticonvulsant drugs. Two days before he died, he apparently had a major seizure in the bathroom at his house. He lay on the floor an undetermined time before being found by his brother who lived next door. He was admitted to Research and Educational Hospitals in a moribund state and died 21 hours later of bronchopneumonia.

Post Mortem Findings

Gross Examination: The brain weighed 1450 grams and appeared essentially normal on external inspection with the single exception of the right posterior tempo-parietal surface (fig. 1). At this site there was a 5 x 4 cm. lesion with small irregular undulations of the surface, suggesting abnormal gyrus formation. Near the center of the area was an indentation measuring 2 x 1.4 cm.

A horizontal cut was made, the plane of section passing through the center of the surface lesion. This showed irregularly thickened cortex lining the depression in the convexity, and normal convolutions replaced by irregular masses of gray matter separated by bands of white matter of varied widths (fig. 2). This condition extended from the surface of the brain to the lateral ventricle, the ependymal surface of which was irregular, reflecting the presence of islands of gray matter underlying it.

Further horizontal cuts at 1 cm. spacings through the inferior portion of the brain showed the lesion to be more extensive than its external appearance had suggested. It extended medially to the lateral ventricle and posteriorly to within 5 cm. of the occipital pole. The right lateral ventricle was smaller than the left, the size of which was not abnormal. The entire left hemisphere, the basal ganglia, thalamus, brain stem, and cerebellum appeared normal.

Microscopic Examination: The thickened cerebral cortex described above was seen to be abnormal. Areas well populated with nerve cells were interspersed with areas relatively free of

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Fig. 1. External aspect of the lesion showing the indentation, suggestion of microgyria, and merger with normal appearing convolutions.
neural elements. Except that these neuron-free areas tended to be in streaks, evidence of organization or cortical stratification was minimal. The abnormal cortex was traversed by more than usual numbers of myelinated fibers with a proportional increase in oligodendroglial nuclei. The neurons ranged from small to medium size, were mature, and, except for their distribution and lack of architectonic stratification, were not remarkable. In the plane of section the abnormal cortex merged with histologically normal cortex on the convexity of the brain about 1 cm. posterior to the Sylvian fissure anteriorly, and about 3 cm. anterior to the occipital tip posteriorly.

The pia-arachnoid had been stripped from most of the convexity over the lesion, but that which remained appeared normal. At one point a dense band of myelinated fibers lay directly under the pia-arachnoid (fig. 3). The islands of gray matter were surrounded by fascicles of both large and small myelinated fibers (fig. 4). Weil and Klüver preparations revealed no abnormalities of myelination.

In the ectopic islands of gray matter dispersed in the centrum semiovale, the absence of architectonic organization was also present (fig. 4). Pyramidal cells had no orientation, one with the other. Individual neurons appeared normal, and the numbers of glial nuclei were not remarkable, with the exception of increase in oligodendroglia related to the myelinated fibers and bundles (fig. 5).

On the convexity of the involved part of the brain, corpora amylacea were numerous. Hematogenous inflammatory cells in cortical vessels of both hemispheres were considered a terminal phenomenon. Sections of other parts of the brain stem were entirely normal.

**DISCUSSION**

The first case report dealing with heterotopic gray masses in the brain is attributed to Tungel in 1859 (1), but, according to van Gieson (2), the term "het-
eratopia” was devised by Rudolph Virchow in 1867. Virchow noted the lesion in the case to be “as if a gyrus was placed in white substance”. This case, plus 12 others in the literature at the time of his writing, and a new case were summarized by Meine (3) in 1898. Some of these 14 cases were essentially of normal intelligence, although many were not, and most were epileptic. Meine’s case was of a mentally defective, hydrocephalic child who began having seizures at the age of 7 years and died at the age of 14 years of aortic insufficiency. In 1930, Kernohan (4) commented on the paucity of cases reported in languages other than German. Further search for reports in the medical literature suggests that most cases of heterotopia are either part of a very gross malformation (such as agyria) or
usually innocent nodular rests on the ventricular wall. Minkowski (5), writing on morphologic anomalies of the gray matter, noted that heterotopias represent a “characteristic and frequent element of microcephalic brains of all kinds”. On the other hand, Norman (6) described heterotopic collections in the centrum semiovale as well as other anomalies in an extraordinarily large brain.

The heterotopias in the case presented here are neither part of a complex cerebral anomaly, nor asymptomatic rests of tissue. It is suggested that the congenital defect characterized by heterotopias of cerebral gray matter and disruption of normal central cortex formation in this case served as a seizure focus, resulting in psychomotor or temporal lobe seizures. The electroencephalogram correlated well with the pathologic specimen. The psychomotor type of seizure, and the aura of “brightness” would direct the clinician to the temporal and occipital lobes.

Reference has already been made to Kernohan (4) who showed that heterotopic rests of neurons could obstruct the aqueduct producing obstructive hydrocephalus. Field et al (7) reported the case of a hemiplegic child who was discovered to have a large mass lesion in one hemisphere and hydrocephalus opposite, the mass clinically was considered to be a tumor. Necropsy showed that the lesion was in fact a large anomaly consisting of heterotopic gray matter.

The gross pathology in the case presented here is strikingly similar to one illustrated by Russell and Rubinstein (8). Their example was from a man, aged 35 years, who had had convulsions since the age of 13 years. He died in status epilepticus. Pathologic changes included scattered ectopic gray masses up to 2.5 cm. in diameter extending from the right frontal pole as far back as the parieto-occipital junction. The lateral ventricle was very irregular and much larger than the left. The left hemisphere, the brain stem and cerebellum were normal. The pathologist who described the material concluded his report with the statement, “This is a remarkable case of ectopia of the gray matter and presumably it was this ectopic gray matter which caused the fits” (9).

The disordered embryogenesis resulting in heterotopias has been described by Bielschowsky and Rose (10), and classified by H. Jacob (11). Presumably, the basic defect occurs in the period of migration of germinal cells from the mantle zone during which there may be an abnormal spontaneous proliferation at or under the cortical mantle. Alternatively, failure of migration would leave islands of cells deep to the centrum in the position of the original matrix layer. In the case presented here, and the comparable English one, one may assume from the subependymal clumps of gray matter bossing the ventricular wall, the islands of gray matter in the centrum semiovale, and depressed but thickened cortex overlying, that a combination of factors applied.

**SUMMARY**

Attention has been directed to the fact that heterotopic gray matter constitutes an anomaly which is not necessarily part of a very gross defect but which may result in clinical symptoms. The pathologic findings in this case, consisting of unorganized islands of nerve cell bodies separated by bands of white matter,
have been described and illustrated. These findings are correlated with the clinical problem and the electroencephalographic abnormality.

REFERENCES