LOCALIZED CEREBRAL GLIOSIS WITH GIANT NEURONS
HISTOLOGICALLY RESEMBLING TUBEROUS SCLEROSIS*

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There are many pathological states which give rise to mental deficiency and convulsive seizures starting at or near birth. Some of these are related to injury at birth; others consist of malformations either genetic in origin, or resulting from injury in the early stages of embryonic development. One group of such pathological states is characterized histologically by the presence in the central nervous system of abnormal, giant, deformed neurons, and/or giant, deformed astrocytes. Most commonly, such abnormal neurons and astrocytes are found in the form of discrete gross nodules, and this entity has been designated tuberous sclerosis (1, 2). Abnormal giant neurons have been described in pachygyria (3, 4), in some cases of von Recklinghausen’s disease (5), and in one case of Albright’s disease (6). More recently Crome (7) has reported the pathological changes in two cases in which the abnormal cells were present in large numbers distributed diffusely in one broad area of one cerebral hemisphere. The purpose of this paper is to describe the clinical and pathological features of a patient with progressive mental deficiency and convulsions since birth in which the similarities to these other conditions and to Crome’s cases, are readily apparent.

CASE REPORT

History: The patient was a 21 year old woman who entered the hospital on May 31, 1958 because of frequent grand mal convulsions, and pulmonary tuberculosis. She had a cousin who was mentally deficient since early infancy, and who experienced grand mal convulsions since the age of 11 years. An uncle of normal intelligence has suffered from grand and petit mal convulsions for many years and has had one transient episode of papilledema during an attack of status epilepticus.

The patient was the first child of a 33 year old healthy woman, and was delivered by forceps after 3 days of difficult labor. The patient weighed 8 lbs. at birth and the neonatal period was described as normal. At the age of one month, she had an episode of fever of undetermined cause. The patient started to walk at 10 months and talked at an early age. At the age of 6 months, she began to have convulsive seizures without obvious cause. The convulsions were sometimes left-sided, sometimes generalized. They occurred every 2 or 3 months during the first few years of her life. At the age of 8 years, the frequency of the seizures had increased considerably, and there were days when she had as many as 40 in a 24 hour period. At this time the seizures consisted of an aura of fright followed by a period of unconsciousness, tonic and clonic movements of the left extremities, upward rolling of the eyes, and incontinence of urine. Often, the clonic movements of the left extremities were followed by clonic movements of the right extremities. The seizures lasted about 1 minute.

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each. At the age of 8 years she was described as a negativistic, friendless child who related only to her mother and always clung to her. She could not attend school, allegedly because of the convulsions; she could not read or write, but could draw rather well. Her vocabulary was very much restricted for her age. Her physical and neurological examinations at that time, disclosed an irritable, poorly developed and markedly underweight child, with deficient left lateral vision and slightly increased deep tendon reflexes on the left extremities. Her gait was awkward, and she was unable to feed herself or control her sphincters well. Skull x-rays and routine laboratory examinations were normal. An electroencephalogram demonstrated diffusely abnormal electrical activity, of moderate to high voltage at a frequency of 3 to 6 waves per second. During the following years, the convulsive seizures were only partially controlled with phenobarbital and dilantin. At the age of 14 years, she developed a rash over the face, trunk, and extremities; this was attributed to the dilantin, and on the discontinuation of this drug, the rash disappeared from the trunk and the extremities, but not from the face. The face had become very oily and revealed a number of papules and pustules, which were diagnosed as acne vulgaris by dermatologists. The following 7 years of her life were characterized by progression of the mental deficiency. Her mental status at the age of 18 years had descended to the moron level with an I.Q. of 52. The seizures continued despite treatment, and she experienced a number of episodes of status epilepticus. Very frequently, before her menstrual periods, she became lethargic, took to bed, and showed very frequent petit mal-like spells. A second electroencephalogram at the age of 16 years revealed a grossly abnormal tracing with a focus of slow waves and large spikes over the right temporal area. At the age of 21 years she was admitted again to the hospital because of recently acquired severe pulmonary tuberculosis and uncontrollable convulsions. She had lost 42 lbs. in the previous 6 months.

**Examination:** On admission, her blood pressure was 100/50 mm of Hg.; her pulse rate 100/min.; her temperature 104.4°F.; and her respiratory rate 18/min. She appeared suspicious, withdrawn, and sullen, refusing food, and answering questions with very short sentences. Her face was flushed, hot, and moist, and exhibited a chronic papular rash. There were a few carious “baby type” teeth in her mouth. Her permanent teeth had never erupted. There were clinical and radiological evidence of tuberculous pulmonary infiltration of the right lung with extensive cavitation. The physical examination was otherwise normal. The blood hemoglobin concentration was 9 grams per cent, with 14,500 white blood cells per cu. mm. and a differential count of 88 per cent polymorphs, 14 per cent lymphocytes and 8 per cent eosinophiles. The tuberculin test was positive, and acid fast bacilli were found in the respiratory secretions.

She was treated intensively with antibiotics, isonicotinic acid hydrazid, and para-amino salicylic acid, with little improvement in her condition. On several occasions she developed severe electrolytic imbalance with marked hypopotassemia (2.6 meq./L.) which persisted despite the intravenous administration of potassium. The high fever continued despite all efforts at control. She became progressively stuporous, and developed jaundice and severe hypotension which required vasodepressors. During this period she showed almost continuous jerks of the facial muscles and of the right extremities. About 1½ months after admission she improved remarkably, became alert, talked and fed herself, and the convulsions ceased. She remained well for a week when again she suddenly became stuporous, and 2 days later lapsed into coma. Her serum sodium concentrations dropped to 119 Meq/L., the serum chlorides to 119 Meq/L., and the serum potassium to 1.7 Meq/L. The liver became palpable below the costal margin, and she died a week later.

**Post Mortem Findings:** At autopsy there was far advanced pulmonary tuberculosis, bronchiolitis obliterans, left lobular pneumonitis, and severe atherosclerosis limited to the coronary arteries. The brain weighed 1070 grams. The posterior portion of the right cerebral hemisphere appeared moderately atrophic when compared to the left. The atrophic areas included the occipital lobe, the parietal lobe, the entire temporal lobe and the cingulate gyrus posterior to the level of the anterior limb of the internal capsule. The cerebral vessels showed no appreciable atherosclerotic changes. The cerebellum and brain stem were normal
externally and on section. Section of the cerebrum revealed the white matter of the atrophic tissues to be shrunken, decreased in size, soft, and gray. Portions of the overlying cortex appeared whitish. Microscopically, there was a marked disorganization of the neuronal cytoarchitecture of the cortex, characterized by a variable, at places marked, decrease in the number of neurons, irregularity in arrangement, and the presence of numerous bizarre, deformed and giant neurons (figs. 1, 2, 3). These neuronal changes were associated with

Fig. 1. Cerebral cortex, left parietal lobe. The neuronal cytoarchitecture is normal. Luxol blue Nissl stain; × 30.

Fig. 2. Cerebral cortex, right parietal lobe. Area symmetrically opposite to that in Figure 1. The neuronal cytoarchitecture is disorganized and large numbers of giant neurons are present. Luxol blue Nissl stain; × 30.
marked astrocytic changes, the astrocytes being increased in number, often markedly hypertrophied, and many being multinucleated and gigantic (fig. 4). In places a gyrus would be focally involved by such changes, with relatively normal appearing cortical areas alternating with abnormal areas (fig. 2). In other places the astrocytic changes would be...

Fig. 3. Cerebral cortex, right parietal lobe. Bizarre, deformed, giant neurons are present. Cajal silver nitrate stain; X 120.

Fig. 4. Cerebral cortex, right temporal lobe. Bizarre giant neurons and giant astrocytes are present. Phosphotungstic acid hematoxylin stain; X 120.
Fig. 5. Central white matter, right temporal lobe. Neurons and astrocytes are present. Axons are present in large numbers in this area in which the myelin is essentially absent. Nissl and Romanes stain for axons; $\times$ 120.

Fig. 6. Coronal section of parietal lobes. There is a marked reduction of central white matter of the right parietal lobe. Weil stain for myelin; $\times$ 1.3.
marked in a zone in which the neuronal changes were slight. Isolated normal, some abnormal and occasionally giant neurons, as well as many hypertrophied, giant, and multinucleated astrocytes were present in the underlying white matter, which revealed in addition a marked reduction of myelin with only a slight loss of axons (Figs. 5, 6). The oligodendroglia were reduced in number; there were no phagocytes and no inflammatory changes in either cortex or white matter.

Both nuclei gracilis revealed loss of neurons and deposition in the tissues of irregular rounded eosinophilic bodies of degenerative material, some of which resembled degenerated neurons. Astrocytosis was minimal, and tract degeneration above or below these nuclei was not demonstrated. The cerebellum revealed a few areas of cortical degeneration affecting the Parkinje and granular cells. These lesions were unlike those in the cerebral cortex, and resembled those which accompany convulsive disorders. There were no changes in the left cerebral hemisphere, or in the other portions of the right hemisphere and the brain stem.

**DISCUSSION**

The essential pathological changes were limited to the posterior portion of one cerebral hemisphere. The most obvious alteration was that of the white matter which grossly resembled diffuse sclerosis (fig. 6). These changes included a marked reduction of myelin sheaths, a much lesser decrease in the number of axons, a moderate proliferation and hypertrophy of astrocytes and the presence of a small number of neurons (figs. 5, 6). The overlying cortical areas appeared pale. Microscopically, the cerebral cortex in the areas overlying the altered white matter, and to a lesser degree in adjacent areas, revealed a disorganization of the neuronal cytoarchitecture, an overall decrease in the number of neurons, the presence of a large number of bizarre, distorted, giant neurons, and a marked increase in the number and size of astrocytes, all with large nuclei, and swollen well stained eosinophilic cytoplasm, some being giant, and some multinucleated (figs. 2, 3, 4).

The cortical changes were essentially identical with those observed in the abnormal nodules seen in tuberous sclerosis, but there were no nodules in the case being reported. All the other characteristic features of tuberous sclerosis were lacking, such as the multiplicity of focal lesions, the nodular character of these lesions or "tubers", the subependymal ridges or "candle gutterings", and the hamartomatous nodules in the skin, kidney, heart, liver, and other visceral organs. Even when the changes of tuberous sclerosis are limited to one or two lesions in the brain, these are individually characteristic of this disease, as in Yakovlev’s case (8). Somewhat similar microscopic changes have been reported in other conditions, such as the giant neurons in pachygyria (3, 4), in one case of Albright’s disease (6), and in some cases of von Recklinghausen’s disease (5). Giant neurons were also reported by Crome (7) in 2 infants in which the mental retardation and convulsions were accompanied by paralysis. In these cases as well, the process was not nodular, but diffuse although essentially involving only a portion of one hemisphere. These cases too were associated with a marked gliotic reaction in the cortex, and in the underlying white matter, the latter being demyelinated. A sibling of one of Crome’s 2 autopsied cases was clinically similar. The other autopsied case is of special interest in that the tissues removed at a left frontal lobotomy prior to death, in an effort to control the convulsions,
showed no such evidence of the marked histological abnormalities observed at autopsy 20 months later, the abnormalities being most intense immediately behind the operative defect. Gliotic changes of much lesser intensity were reported involving the brain stem, cerebellum, and the opposite hemisphere.

Tuberous sclerosis and von Recklinghausen’s disease are certainly congenital conditions genetic in origin, while the onset of symptoms at or near birth in the other conditions indicate that these, too, are congenital in nature. The second and third cases in Crome’s report (7) are siblings, with similar clinical and presumably histological changes, so that these may also be genetic in origin. On the other hand, the relationship of the area of the most intense histological change in Crome’s first case, to the surgical excision, clearly indicates that the process was intensified, if not initiated, by the surgical trauma. In the case being reported, there is a history of difficult and prolonged labor, while a genetic factor is at least suggested, by the occurrence of mental deficiency and convulsions in one cousin, and convulsions in one uncle. If we acknowledge that acquired injury, such as the operation in Crome’s first case, or the difficulties in childbirth in our case, plays a role in the pathogenesis of these bizarre changes, it must also be acknowledged that this injury must act upon an altered neurologic substrate presumably genetic in character. While birth injury is common, histologic changes like those under consideration, appear to be quite rare. One may conclude that birth injury alone will not result in the pattern of pathologic changes being described. In Crome’s second case, the genetic factor was not associated with known trauma. The neuronal cytoarchitectural disorganization and the giant bizarre neurons were most likely present since birth, or shortly thereafter. The large hypertrophied and bizarre astrocytes may have similarly remained unchanged since birth, and may similarly be the result of the genetic factors postulated. Histologic evidence of continuing activity of the pathological process at the time of death, in the form of phagocyte formation or inflammatory changes, was not evident. The absence of myelin in the subjacent white matter warrants special emphasis in view of its severity and its lack of association with axon destruction, features reminiscent of the demyelinating diseases but not restricted to them. The presence of neurons in the white matter strengthens the possibility of the entire process being genetic. The histological changes in the medulla oblongata bear no resemblance to those found in the cerebrum; they are apparently recent and their significance is not clear.

Of interest is the absence of pathological changes in the left hippocampal gyrus, despite the large number of convulsive seizures and numerous episodes of status epilepticus, over a period of 21 years. On the other hand, the cerebellum did show areas of cortical degeneration of a type commonly found in patients with convulsions.

The exacerbation of clinical symptoms at puberty and in the premenstrual periods, may reflect the effect of an altered hormonal and physiological state, upon an unchanging basic neural defect. A similar situation is not infrequent in patients with tuberous sclerosis. In the presence of a severe and extensive pathological process of a large part of the right cerebral hemisphere, the absence of a
hemisensory syndrome is of clinical interest. While it is possible that a more precise and detailed examination might have shown a neurologic defect, it is also possible that there was none since a large proportion of the axons of the affected areas was preserved, only their myelin sheaths being absent. The electroencephalogram, on the other hand, consistently indicated right-sided cerebral pathology with a temporal lobe focus of dysfunction.

Parenthetically, the severe coronary arteriosclerosis in the absence of similar involvement of other vessels remains unexplained.

SUMMARY

This report deals with a 21 year old woman with progressive mental deficiency and convulsions since birth. At death, degenerative changes were noted in the cortex and white matter of a major portion of the right cerebral hemisphere, the right frontal lobe and the left cerebrum being normal. The changes consisted essentially of a disruption of the cortical architecture, and the presence of large numbers of abnormal giant neurons and astrocytes in the cortex and to a lesser degree in the white matter, the latter containing very little myelin but an approximately normal number of axons. The process, although limited to one cerebral hemisphere, was not nodular, but diffuse in the affected area. The relationship between the case reported and other conditions that may be associated with abnormal giant neurons such as tuberous sclerosis, pachygyria, von Recklinghausen’s disease, and Crome’s cerebral gliosis is discussed. It is suggested that the changes described were due to an abnormality in embryologic development prior to birth, and might possibly be genetic in character, although the process may have been intensified by injury at birth.

REFERENCES