EPILEPSY DUE TO BIRTH INJURY IN ONE OF IDENTICAL TWINS

BY

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One of the most cogent arguments used in favour of an inherited constitutional factor in the causation of idiopathic epilepsy is the finding that, if one of a pair of identical twins has fits, it is usual for the other to have frank epilepsy or at least an abnormal electroencephalogram (Lennox, 1947; Little and Weaver, 1950). Cerebral disease or injury, including birth trauma, may lead to epilepsy either by damaging a hitherto normal brain or, perhaps by a less severe lesion, by reducing the convulsive threshold in a predisposed individual. According to Nielsen and Courville (1951) the latter situation is much the commoner, and in Lennox's series of identical twin pairs in which one twin suffered from epilepsy following brain injury no less than half the non-epileptic co-twins had abnormal electroencephalograms. None of these studies was concerned with the pathology of the underlying birth trauma and we have thought it of interest to record the neuropathological findings in the following case of a child, the second of identical twins, who had suffered from what seemed to be a moderate degree of birth injury which had resulted in mental retardation and epilepsy. The child died after being in status epilepticus and only microscopical changes were found in the brain. The surviving twin is normal both clinically and electroencephalographically. It is noteworthy that such a gross degree of functional defect could be brought about in a child without genetic predisposition by a birth injury that failed to produce any gross distortion of brain structure.

Case Report

Mrs. P., a primigravida aged 24, had an uneventful pregnancy (apart from the recognition of twins in January) till May, 1950, when she developed pre-eclamptic toxæmia. As she was only a week from her expected date of delivery, medical induction was undertaken and labour began. After eight hours it was deemed advisable to rupture the membranes and meconium-stained liquor was obtained. The first twin was born by the vertex rather less than two hours later; he was in good condition and cried well. Ten minutes later the membranes of the second twin were ruptured and again the liquor was stained with meconium: this baby was delivered by breech extraction with some difficulty and was slow to cry. Soon after the second twin a single, uniovular placenta was expelled intact. The first twin weighed 4 lb. 14 oz. at birth, and the second 5 lb. 3 oz. Both babies were in an oxygen tent for the greater part of the first two days, this being the routine for premature babies at that time.

Apart from physiological jaundice, the smaller twin (Julian) made normal progress in the neonatal period and has continued to make normal progress ever since. The second and larger twin (Roger) after 48 hours was noted to have periods of very poor colour and was jaundiced, the hands and face twitched and he breathed irregularly. The rectal temperature was 103·6°F. and penicillin was therefore prescribed. As the fontanelle was not tense and there was no neck stiffness, lumbar puncture was not performed, but chloral, grain $\frac{1}{2}$, was given every half hour till twitching ceased. Vitamin K and subcutaneous glucose were administered in addition. That evening the temperature (rectal) reached 105·6°F.

During the next three days, the temperature fell, colour improved and there was no recurrence of twitching: feeding was satisfactorily established and intramuscular penicillin was stopped, though oral dosage was continued for another six days. Oxygen was intermittently administered for the first week of life.

Both twins had regained their birth weight by the fourteenth day, when they were discharged from the maternity hospital. Both were artificially fed. Right from this early date Roger was difficult with bottles and made slower progress than the smaller twin. Nevertheless, Roger was attempting to sit up and seemed to be able to recognize his parents at the age of 16 months. He then developed a cough with a tendency to vomit and had a fit in which he became blue, limp and unconscious. He was rushed to hospital where he was found to be barely febrile (100·2°F rectally), although he was still twitching. The convulsion was easily controlled with intramuscular paraldehyde, but twitching recurred briefly later the same day. The cerebrospinal fluid was normal. No focal neurological signs were found and no
diagnosable infection developed. The child's mental retardation was all too obvious and he was discharged after five days.

There was some regression after this illness: he ceased attempts to sit and seemed less sure in his recognition of his parents. Progress was slowly resumed, however, and he learned to make some attempts at speech and to walk around the furniture. From the date of this illness he was constantly under hospital supervision and received anticonvulsant therapy. He had to be readmitted, however, on a number of occasions because of further convulsions.

In November, 1951 (aged 18 months), there was a suggestion of left-sided hypertonus, and both plantar responses were extensor. The cerebrospinal fluid was again normal.

In October, 1952, the left side seemed hypotonic after the fit, but all reflexes were symmetrically diminished.

In March, 1953, the convulsion was mainly right-sided, but on recovery no neurological abnormality was found. Plantar responses were flexor. In July, 1953 (aged 3 years 2 months), bilateral convulsive movements started at 7 a.m. and intermittent twitching occurred throughout the day in spite of therapy. He vomited some altered blood and his temperature rose inexorably. After two days he developed pulmonary oedema and died.

No electroencephalogram was ever attempted on Roger. He was too retarded to be likely to cooperate and the fact of epilepsy was hardly in doubt. There was, furthermore, no focal sign to suggest a lesion which might be surgically treated. An E.E.G. was undertaken on Julian, however, at the age of 4 and was reported as giving a tracing within normal limits for the age.

Evidence of Identical Twinning

Both boys were examined closely from this point of view in February, 1952 (aged 21 months), and were found to be 'identical' in general body configuration, in the colouring of hair and eyes, in iris pattern, in ear shape and in dental structure. The palmar creases were very closely similar and the fingerprint patterns were very similar in all four hands. Blood groups were investigated by Dr. R. A. Zeitlin, to whom we are grateful for the following results:


The finding of the intact uninuovular placenta is also most important. It is, therefore, overwhelmingly probable that these boys were uninuovular twins and were genetically identical.

Necropsy Report of Roger

There was some excess of glairy exudate in the main air passages but no pneumonia and no cause was found to explain the fever. The brain looked entirely normal.

Brain. The brain weighed 983 g., of which the cerebellum and brain-stem accounted for 127 g. The vertex had become flattened during the process of fixation, but it was evident that the gyral pattern was normal and there were no signs of convolutional atrophy or localized softening. The corpus callosum, however, was unduly thin. Blocks of tissue were taken from representative parts of the cerebral cortex, basal ganglia, cerebellum and brain-stem. Celloidin and frozen sections were prepared and stained for nerve cells, myelin, fibrous neuroglia and lipid.

Cerebral Cortex. Many parts of the cortex showed extensive areas in the third layer from which the great majority of the nerve cells had disappeared. In the temporal and occipital lobes the second layer was also frequently affected so that the larger pyramidal cells of the third layer often appeared to be the most superficial portion of the remaining cortex (Fig. 1). A similar type of incomplete laminar atrophy, though less widespread, was present in the region of the frontal poles (Fig. 2) and in the right insula. There was frequently a tendency for the depths of the gyral walls to be more affected than the crowns of the convolutions and in both visuo-sensory areas (O.C.) only the walls of the calcine fissures were involved. On the right side the pyramidal cell layer of the uncus (Fig. 3) and of Ammon's horn in its Sommer sector were partially atrophied, the amygdaloid nucleus being unaffected. The hippocampal gyrus was intact. In all these areas of atrophy there was an overgrowth of the astroglia, but the overlying molecular layer did not show a severe marginal gliosis of the Chaslin type. The cortex was generally congested and the smaller blood vessels were unduly numerous in the areas of devastation. In some of these damaged gyri the medullary cores showed a mild diffuse loss of myelinated fibres, though elsewhere the staining of the central white matter appeared adequate for a child of this age. There was, nevertheless, a well-marked generalized fibrillary gliosis of the white matter, the density of which was unrelated to the degree of myelination. For example, in the left precentral gyrus where the myelination of both grey and white matter was particularly good and where there was no apparent diminution in the number of nerve cells, the gliosis of the central core was especially dense (Figs. 4 and 5). Small groups of fat-granule cells were occasionally seen around vessels in the cerebral white matter, but otherwise there was no indication of microglial activity. In addition to these longstanding lesions the cortex showed considerable recent damage attributable to the terminal status epilepticus. 'Areas of paling' of irregularly laminar distribution were present, mainly in the deeper part of the grey matter. In these areas the ground substance was rarefied or vacuolated, the nerve cells showing severe shrinkage and liquefaction with condensation of their basophil material into crenated formations. Spielmeyer's ischaemic nerve cell change was sometimes seen and some cells exhibited incrustation of the Golgi network.

Basal Ganglia. In the thalami the dorso-medial and the ventro-lateral nuclei showed extensive loss of
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Cerebellum. Fibrillary gliosis was found in the white matter, but it was less conspicuous than in the cerebral hemispheres. Myelination was normal and the Purkinje cells present in normal numbers in the vermis and lateral lobes. Both dentate nuclei showed minor nerve cell losses.

Brain-stem. The midbrain and pons appeared to be intact. In the medulla the inferior olives showed an abnormal gliosis in both the grey matter and the hila without associated cell loss. The pyramidal tracts were normal.

Discussion

Since it is unlikely that the patient's presumed neonatal infection or mild jaundice could have caused the extensive neuronal destruction found in his brain, it may be assumed with some confidence that an injury at birth had taken place, particularly in view of the breech delivery and the general retardation in the infant's development compared with the progress of the healthy identical twin. The absence of a genetically conditioned cerebral dysrhythmia, as proved by the surviving twin's normal electroencephalogram, indicated that the damage inflicted on the brain had been sufficient in its own right to cause the severe epilepsy from which this child suffered. The case was not, therefore, one in which birth injury had lowered the convulsive threshold of a predisposed individual.

The brain, however, showed none of the macroscopic features presented commonly by the late sequelae of birth trauma, there being no cystic softenings or sclerotic microgyria (Benda, 1945, 1952; Norman, 1953). The histological findings had some points of resemblance to the 'diffuse patchy cortical devastation' described by Benda in cases of birth injury and attributed by him to venous stasis. In this group, however, additional sub-cortical and striatal lesions

nerve cells with accompanying increase of glial nuclei and fibres. The right subthalamic nucleus appeared normal, as were each putamen and globus pallidus.

Fig. 1.—Right middle temporal gyrus showing diffuse loss of nerve cells in L2 and L3. Carbol azure \( \times 60 \).

Fig. 2.—Left frontal polar cortex showing diffuse loss of nerve cells in L2 and L3. Carbol azure \( \times 60 \).

Fig. 3.—Right uncu showing sectional losses in the pyramidal nerve cell layer (at *). The hippocampal gyrus is intact. Carbol azure \( \times 6 \).
were usually present and the areas of cortical neuronal necrosis were more irregularly distributed than the essentially laminar lesions in our case. Diffuse atrophy of the third cortical layer is common to many anoxic and ischaemic conditions (Courville, 1953) and the segmental lesions of the pyramidal cell layer of the uncus and cornu Ammonis are also well known sequelae of anoxia. There was no sclerosis of the hippocampal gyrus itself in our case so that it is unlikely that the changes in the right temporal lobe were the result of herniation of the hippocampus into the tentorial incisura, a mechanism recently described in certain cases of birth injury by Earle, Baldwin and Penfield (1953). The simplest interpretation of the pathological findings in this brain would therefore be that they followed birth anoxia with its associated circulatory disturbances.

There remains, however, the problem of the possible relationship of the brain damage to the patient's epilepsy. Scholz (1951) has convincingly shown that widespread neuronal destruction of a selective character may follow the functional vascular disturbances which are associated with fits, especially when these occur in young individuals. The pattern of these lesions closely resembles that produced by cerebral anoxia and includes laminar cortical atrophy, sclerosis of Ammon's horn, gliosis of the white matter and areas of nerve cell loss in thalamus and dentate nucleus—all structures affected in this brain. Perhaps the involvement of the calcarine cortex in our case is a small pointer in favour of a primary birth injury, since this area is often spared in a remarkable way in epilepsy. However, it would also be true to say that birth anoxia often damages the corpus striatum, which was a centre unaffected in this case.

The evidence is therefore equivocal, and clear-cut distinctions between these two varieties of destructive process may be impossible on histological grounds alone. Apart from the changes produced by the terminal status epilepticus, there was no evidence of recent brain damage, such as neuronophagia or microglial activity, which might have suggested the effect of a recent seizure; nor did the clinical picture indicate a progressive cerebral atrophy. Nevertheless, it is undeniable that the first major attack at 16 months caused a setback in the child's developmental progress, so that he lost some of his hard-won abilities such as sitting and standing and found great difficulty in regaining them. It is, therefore, not improbable that some additional structural damage was inflicted at this time. Scholz's (1951) cases of post-epileptic neuronal necrosis were considered to be examples of idiopathic epilepsy and in several there was a family history of fits. The present case suggests that symptomatic epilepsy due to birth injury may have similarly dangerous potentialities.

Summary

The neuropathological findings have been described in a case of birth injury affecting one member of a pair of identical twins. The injured twin was mentally defective and epileptic, while the co-twin is healthy and has a normal electroencephalogram. The brain showed no naked-eye abnormality, but microscopically there was widespread longstanding neuronal atrophy involving mainly the outer cortical layers, the cornu Ammonis and thalami. It is considered that most of these lesions occurred at the time of birth, but that additional brain damage may have followed a severe fit in infancy.

References