CEREBRAL MICROGYRIA IN A 27-WEEK FETUS: AN ARCHITECTONIC AND TOPOGRAPHIC ANALYSIS*

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ABSTRACT

The cytoarchitecture and topography of a case of restricted cerebral microgyria in a 27-week fetus are analyzed in whole brain serial sections. The cytoarchitectonic features of the four microgyric layers and their continuity with the layers of normal cortex imply that microgyria is the result of a post-migratory encephaloclastic event resulting in laminar destruction of the middle cortical layers. The distribution of the abnormality in this and other cases suggests that the etiology of this laminar destruction may be intra-uterine hypoxia or perfusion failure.

INTRODUCTION

Microgyria (micropolygyria, polygyria) of the cerebral cortex is a developmental abnormality characterized by excessive surface convolution. It is among the relatively common malformations associated with mental retardation being found in 27 (5%) of 500 consecutive autopsies on mental defectives (11).

The authoritative studies of Bielschowsky (5, 6) have dominated subsequent views of the morphogenesis of this malformation (9, 11, 12, 22, 23). Bielschowsky felt that the architectonic features of microgyria point to an arrest of neuronal migration. An opposing view, that microgyria is a malformation of post-migratory cortex (4, 13, 17, 21), has not been widely accepted. It is based upon architectonic observations and interpretations that differ fundamentally from those of Bielschowsky (17).

The cytoarchitectonic features of microgyria basic to an evaluation of these two opposing theories are considered critically in the present study of a 27-week fetus, to our knowledge, the youngest specimen with microgyria reported in the neuropathological literature. The cytoarchitectonic findings typical of microgyria are explicit in this case, at an age when the convolutional pattern of both normal and abnormal areas is relatively simple. Our observations support the view that microgyria is the result of an event occurring after the completion

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of neuronal migration. In addition the topographic distribution of the defect, in
both a radial and tangential sense, suggests a plausible pathogenic mechanism.
These conclusions regarding the timing and the mechanism of the pathogenic
event in microgyria extend also to the more complex cerebral malformations
of which microgyria may be a part, e.g., porencephaly-hydranencephaly (18) and
occipital encephaloleccele (7).

**METHODS**

The formalin-fixed whole brain (Harvard-Warren Museum #RPSL-W-222-65) was
embedded in celloidin and sectioned serially at 35 microns in the horizontal plane by
the method of Yakovlev (27). Every tenth section was stained for myelin by the Loyez
method and the adjacent sections for cells with cresyl violet. Every hundredth section was stained
with hematoxylin and eosin. Age-matched controls prepared in the same manner were
available for comparison from the Harvard-Warren Museum collection. Drawings were
made with a calibrated Leitz drawing tube attachment.

**CASE DESCRIPTION**

*Clinical History and Gross Findings.* (Boston Lying-In Hospital #A65-103). This male
infant was the product of the fourth pregnancy of a 27-year old gravida IV, para III
housewife. Three older children were normal and previous pregnancies had been uneventful.
The mother had been under regular prenatal surveillance from the end of the second month
of pregnancy. The pregnancy was uneventful until the 29th week, as estimated from the last
menstrual period, when labor began suddenly with vaginal bleeding suggesting abruptio
placentae. The Apgar score was 1 at delivery and 4 at five minutes. From birth the infant
was markedly hypotonic and areflexic. Despite intubation, oxygen, bicarbonate and anti-
biotics he remained cyanotic and expired after three and one half hours.

At autopsy the total body weight was 1250 grams and the crown-rump length was 23.5
cm, a value consistent with a gestational age of 27 weeks, approximately two weeks less
than the gestational age estimated from the last menstrual period. Abnormal findings from
the general examination were limited to manifestations of perinatal hypoxia and extreme
prematurity: hemorrhages in the adrenals, bowel and subarachnoid space, and immaturity
of the lungs and kidneys. The placenta was partially circummarginate. An old large
hematoma suggested a clinically unrecognized previous abruptio.

The fresh brain weighed 175 grams. The right cerebral hemisphere (figs. 1A and 1B) was
the site of a grossly apparent abnormality with a reduction in the bulk of the frontal and
parietal lobes, and the superior portion of the temporal lobe. The characteristic partially
developed convolutional pattern of a 26-27 week fetus, present in the normal left hemi-
sphere, was replaced in these regions by a granular or cobbled surface. Except for a
reduction in size of the right basis pontis, the gross appearance of the remainder of the
brain was normal.

*Histological Analysis from Whole Brain Serial Sections.* The area of cortical abnormality
was limited to a single region of the right hemisphere centered on the Sylvian area and
included the insula, the lateral and medial surfaces of the frontal and parietal lobes, and the
superior portion of the temporal lobe (figs. 1C & 4B). The cytoarchitectonic and convoluc-
tional abnormalities were most severe in the topographic center of the lesion and least
severe where the defective cortex merged with normal cortex.

The four cortical layers classically described by Bieschoswsky (5) were evident in most of
the microgyric area (fig. 2A): 1) molecular layer, 2) outer cellular layer, 3) cell-sparse layer,
4) inner cellular layer. The abnormal cortex was markedly undulating (fig. 1C) with many
irregular small gyri projecting in various planes. This pattern was most marked in the outer
cellular layer, with the cell-sparse and inner cellular layers involved to a lesser degree. The
molecular layer was also less convoluted and in many places where the deeper layers were
markedly redundant, the molecular layer was almost uninvolved, giving the surface of the brain a paradoxically flat appearance (fig. 1C).

The molecular layer was narrowed and mildly hypercellular. The outer cellular zone, the second microgyric layer, consisted of at least two, and in some places three, readily recognizable sublayers (fig. 2C). Most superficially lay a narrow band of small, darkly staining, densely packed pyriform cells. Beneath this was a wider band of larger, less densely-packed pyriform cells. In the more differentiated areas of the abnormal cortex (fig. 2B), the radial alignment and large apical processes of these cells could be seen. Near the junction of abnormal with normal cortex, a third deeply situated sublayer was present consisting of a narrow band of small, densely packed cells without evident radial alignment.

Fig. 1A and 1B. Superior and right lateral views of the formalin-fixed gross specimen, with leptomeninges partially removed, showing area of microgyria in the mid- and anterior portions of the right cerebral hemisphere. Note the prominent Ecker's lobule present in the left hemisphere. × 0.8.
or apical processes (fig. 2C). The inner cellular zone, microgyric layer 4, consisted of cells which were more variable in size and shape and were metachromatie in their staining (fig. 2C). These four laminar subdivisions, the three sublayers of the outer cellular zone along with the narrow inner cellular zone, were continuous with layers II, III, IV, and VI respectively of adjacent normal cortex, with which each was cytologically identical (figs. 2A and 2B).

The cell-sparse zone lying between the outer and inner cellular layers contained a few scattered cells (fig. 2C). Also within this zone were occasional small islands of cells (fig. 2B) which appeared to surround radially penetrating venules and capillaries. These cells were large pyramids resembling those of normal layer V. The cell-sparse zone abutted upon the
Fig. 2A. Transition between four-layered microgyric cortex (left) and normal six-layered cortex (right) in the posterior parietal region of the right hemisphere. Note the continuities between layers of microgyric cortex and those of normal cortex. C.V. × 30.

Fig. 2B. Transition between normal (left) and microgyric (right) cortex in the superior insula of the right hemisphere. Cellular differentiation is relatively advanced in this region. An island of pyramidal cells persists within the microgyric clear layer (arrow). C.V. × 42.

Fig. 2C. Four-layered microgyric cortex of the right posterior parietal region at higher power. The apposed molecular layers of each side of a "microsulcus" are fused. The outer cellular layer is composed of three sublayers. C.V. × 42.
middle layers of normal cortex, although the exact level was somewhat variable. In the posterior margin of the abnormal region (figs. 2A and 3A) this layer was continuous with normal layer V. In the inferior margin, it was continuous with either the lower portion of normal layer III or normal layer IV (fig. 2B). Careful examination of serial sections established that at no point was there continuity of this zone with the subcortical fiber zone of normal cortex.

A more atypical microgyric cortex was found in the topographic center of the lesion, the parietal operculum and superior insula. The abnormal convolutional folding of the deep cortical layers here was markedly exaggerated while the surface of the brain was paradoxically smooth. The outer cellular layer was not sublaminated but rather consisted of four or five irregular undulating bands of densely packed cells interrupted by scattered acellular pockets. In places (fig. 3B), the cell-sparse zone, microgyric layer 3, could not be recognized.

Many large islands of cortical cells (fig. 3A) were seen just below the microgyric cortex. These represented tangential sections through deeply infolded microgyric convolutions (internal microgyria) and not subcortical heterotopias, as was easily ascertained by study of serial sections. Scattered single neurons were present in the white matter of normal and abnormal regions, but there were no true subcortical or periventricular heterotopic cell masses.

The white matter underlying the abnormal cortex and the right internal capsule, cerebral peduncle, and corticospinal tract were all moderately reduced in volume. There was a mild increase in vascularity in the abnormal cortical regions especially in the cell-sparse zone, with many dilated, thin-walled, radially running venules and capillaries. The structure of the principal intracranial vessels was normal and all were patent; however, the extracranial

**Fig. 3A.** Three consecutive serial sections from the microgyric posterior parietal region of the right hemisphere. Apparent subcortical cellular islands (arrows) in the section on the left prove to be tangential sections through deeply invaginated microgyri. C.V. × 15.
arteries were not available for examination. The meninges, ventricular system, and the remainder of the forebrain, brain stem, and cerebellum were normal.

DISCUSSION

The present case is that of a 27-week fetus, as estimated by crown-rump length, that was delivered prematurely because of abruptio placentae. The brain is essentially normal except for a large area of microgyria in the right hemisphere, and a reduction in volume of the associated fiber tracts.

The cytoarchitectonic features of the four microgyric layers in this case, as well as their continuity with the layers of normal cortex, permit an evaluation of the timing of the pathogenic event in this malformation. The outer and inner cellular layers are composed of sublayers which are continuous with and cytologically identical to layers II, III, IV, and VI of normal cortex, an observation made originally by Nieuwenhuisje (21) and subsequently by Jacob (17), Bertrand and Gruner (4), and de Leon (13). The cell-sparse zone is continuous with the middle layers of normal cortex, a finding also observed in many previously reported cases (9, fig. 5; 13; 17; 21; 22, fig. 6.43). In none of the serial sections can we confirm Bielschowsky's (5, 6) observation of a continuity between the cell-sparse layer and the subcortical U-fibers which led him to conclude that microgyria is the result of an arrest of neuronal migration. He viewed the cell-sparse zone as the inner limit of the "true cortex" and the inner cellular zone as a layer of heterotopic neurons arrested in their migration. Jacob (17), aware of the implications of the differences between his observation and Bielschowsky's, demonstrated conclusively in his own extensive material, as well as in a re-examination of Bielschowsky's own cases, that the cell-sparse zone is in fact continuous with the middle layers of normal cortex. Jacob
concluded that the deep cellular zone is not heterotopic but is made up entirely of post-migratory cells.

The fact that microgyric cortex (fig. 4A) is made up of cells of layers II, III, IV, and VI, present in normal post-migratory topological relationship to each other, suggests that microgyria is the result of a post-migratory event (4, 17, 21). This view based on histology alone is strengthened (13, 24) by the concept, derived from recent autoradiographic studies (1, 3, 25), of an “inside-out” sequence of cellular migration to the cerebral cortex. That is to say, later-migrating cells take up positions superficial to earlier-migrating cells. The presence in microgyria of the most superficial and hence latest-migrating cells (layer II), along with the deepest and hence earliest-migrating cells (layer VI), suggests that the highly interdependent steps of migration were completed normally and that the microgyric cortex was fully-constituted at some point in time.

Migration of neurons to the cerebral cortex is essentially completed by the sixteenth week (reviewed in 26), so that the pathological process which produces microgyria must occur after that time. In the present case it must have occurred prior to the 27th week, the age at death. This estimate of the time of origin of microgyria based wholly on morphological evidence is corroborated by the two reported cases of microgyria occurring in infants in which there was documented maternal carbon monoxide poisoning in the twentieth (15) and twenty-fourth (2) weeks of pregnancy. Microgyria was present in none of the seven reported cases of carbon monoxide poisoning occurring after the seventh month of gestation (2).

The architectonic findings in the present case permit an evaluation of the nature of the pathogenic process. The four-layered microgyric architecture (fig. 4A) may be viewed as being derived from normal six-layered cortex by the superimposition of a layer of cell-clearing in the region corresponding to layer V. Except for the few scattered islands of cells surviving to mark their previous location, the cells of layer V are completely missing from the abnormal cortex. The fact that cells are actually lost from the cortex suggest that the clear layer represents a zone of destruction rather than a mere separation of the outer and inner cellular layers as has been previously proposed (13, 17, 21). Possibly the destruction of the mid-region of the cortex during a critical period disrupts normal convolutional development and results in the excessive convolutions characteristic of microgyria.

This pattern of a layer of cell loss variably involving the middle cortical layers and associated with an increased vascularity in the same region resembles the morphologic picture of cerebral laminar (pseudolaminar) necrosis (8, 22), an encephaloclastic lesion frequently recognized in perinatal and adult neuropathology. The pathogenesis of laminar necrosis is hypoxia, either ischemic or asphyxial (8, 22). The cases of microgyria resulting from intra-uterine carbon monoxide poisoning (2, 15) suggest that microgyria has a similar pathogenesis.

The topography of the abnormality in the present case is also consistent with
Fig. 4A. Camera lucida drawings to the same scale of normal (left) and microgyric (right) cortex. Roman numerals correspond to the cellular layers of normal cortex. × 70.

Fig. 4B. Modified Mercator, or two-dimensional, projection of the cortex of the entire right hemisphere with basal regions inferiorly and the medial hemispheric surface superiorly. The courses of the three principal cerebral arteries and their major branches are superimposed. Microgyrie regions are dotted with the density of the dots denoting the severity of the cytoarchitectonic abnormality.
this view of pathogenesis. The area of abnormal cortex (fig. 4B) corresponds to
the core territory of the cortical branches of the right internal carotid artery.
This type of presumed vascular topography, more often seen bilaterally, has
been reported frequently in microgyria, especially in cases associated with
porencephaly (4, 6, 9, 12, 16, 18, 19). Dekaban (12) and Levine, Fisher, and
Caviness (18) have suggested that both microgyria and porencephaly may be
due to disturbances in arterial perfusion, with porencephaly the result of severe
ischemia and microgyria the result of mild ischemia.

In the central, and presumably most severely damaged, portion of the micro-
gyric region of the present case, an atypical architectonic pattern is encoun-
tered: the sublamination of the outer cellular layer cannot be discerned, and in
some locations even the classical four-layered architecture is not present. It is
possible that this atypical cortex is part of a spectrum of abnormalities, similar
to that proposed by Courville (8) for the perinatal period, resulting from
cortical insults of varying severity. A minor insult to developing cerebrum
could result in cortical laminar damage and "classical microgyria." A greater
insult, perhaps to the full thickness of the cortex (in a manner similar to
perinatal selective cortical necrosis), might result in "atypical microgyria." More
severe injury (18), damaging the full thickness of the hemispheric wall,
may result in porencephaly.

The present study cannot establish the etiology of the proposed hypoxie or
ischemic event. We might speculate that in cases with a presumed vascular
topography, occlusion of one or more major cortical vessels could have oc-
curred, but evidence for such an event has never been reported. In the cases
associated with carbon monoxide poisoning, and in the present case with the
finding of an old placental hematoma, the possibility is raised of intra-uterine
asphyxia resulting in hypoxia or systemic perfusion failure. However this
mechanism alone does not explain the distribution restricted to the territory of
a single major vessel. Finally the relationship of microgyria to intra-uterine
infection by cytomegalovirus (10, 14, 20) or toxoplasma (13) is not clear. The
architecture and topographic distribution of the microgyria in these cases is
similar to those unrelated to infection. Possibly these morphologic changes have
been produced indirectly by the infection, through fetal hypoxia or perfusion
failure.

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