Polymicrogyria

Jill E. Thompson, Mauricio Castillo, David Thomas, Michelle M. Smith, and Suresh K. Mukherji

From the Departments of Radiology (J.E.T., M.C., M.M.S., S.K.M.) and Pathology (D.T.), University of North Carolina School of Medicine, Chapel Hill

The term *polymicrogyria* refers to the abnormal macroscopic appearance of a portion of the cerebral cortex characterized by too many small convolutions, simulating Moroccan leather. Commonly, polymicrogyria is composed of small irregular gyri without intervening sulci or with intervening sulci obliterated and bridged by fusion of their superficial cellular layers (particularly the molecular one). Occasionally, polymicrogyria may have many small or widened gyri separated by shallow sulci (microsulci) (1). Histologically, polymicrogyric cortex is composed of a heterogeneous collection of neurons and derangement of the normal six-layered laminaion (2). Because of the macroscopic and histologic variations found in polymicrogyria, the term *nonlissencephalic cortical dysplasia* may be more appropriate.

Clinical History

The patient was a 20-year-old woman with a history of asthma and long-standing focal motor seizures; she was found dead in her bed. Six months earlier, the patient had had magnetic resonance (MR) imaging study of the brain at an outside institution (Fig 1). This study showed an area of dysplastic cortex involving the right posterior and superior temporal lobe and extending into the parietal region. The ipsilateral sylvian fissure was prominent. Superficial to the dysplastic cortex, abnormal vessels, believed to be related to prominent veins, were present. The underlying white matter was normal. Postmortem examination revealed hyperinflated lungs with abundant mucus in the bronchial tree. No other specific organ abnormalities were identified. Examination of the brain showed a cavum septum pellucidum, normal-sized ventricles, an open right sylvian fissure, and abnormal sulcation of the right frontal, insular, lateral parietal, and temporal regions (Fig 1D and E). The abnormal cerebral cortex was characterized by shallow sulcation. The cerebellum was normal in size. After fixation, the brain was sectioned into 5- to 10-mm slices in the coronal position in order to match the coronal MR images as much as possible. Sections were made of the abnormal areas and stained with hematoxylin-eosin and Nissl stain. At low power, the abnormal cortex showed shallow sulci, which were fused in the majority of their course (Fig 1F). Nissl stain showed no normal lamination and complete neuronal disorganization (Fig 1G and H). The findings were compatible with polymicrogyria of the unlayered type. The cause of death of the patient was assumed to be related to the seizures.

Discussion

The bilateral cerebral vesicles appear at approximately 35 days of gestation and later...
Fig 1. A 20-year-old woman with polymicrogyria.

A, Coronal T1-weighted MR image (400/15/2) shows wide right sylvian fissure (S). The cortex (p) in the right parietal region is slightly thick and lacks sulci, suggesting a dysplasia. The right cerebral hemisphere is small.

B, Proton density–weighted MR image (4000/19/1) shows thick insular cortex (p). Note prominent vessels in right sylvian fissure, which may be either disorganized branches of the middle cerebral artery or uncondensed veins.

C, Axial T2-weighted MR image (4000/90/1) shows posterior continuation of the right sylvian fissure, which is lined with thickened cortex (p). Note anomalous venous drainage into uncondensed cortical veins. There is scalloping of the inner table of the skull caused by pulsations of cerebrospinal fluid. No signal intensity abnormalities were present in the white matter.

D, Diagram illustrating the cortical dysplasia at the same level as A and E shows thickened dysplastic cortex (P) and a wide right sylvian fissure (S). The square (3) denotes the region from which the microscopic specimens in F through H were obtained.

E, Fixed brain section. Coronal slice corresponding to A shows dysplastic cortex (p). The right cerebral hemisphere is smaller than the left one and the ipsilateral sylvian fissure (S) is wide.

F-H, Microscopy.

F, Low-power view shows very shallow sulci (arrowheads). The pial vessels (small arrows) are deep in the abnormal cortex, following the expected course of the sulci, which are fused in this specimen. Note that surrounding these vessels there is slight cellular paucity, which corresponds to the molecular layer (layer 1) (hematoxylin-eosin, magnification ×10).

G, Low-power view of different area of the same specimen again shows superficial arteries (arrowheads) in shallow cortical sulci, which are fused thereafter at the level of the molecular layers. Note the penetrating arteries and veins (small arrows) at the expected course of the sulci (Nissl, magnification ×10).

H, High-power view shows that the neurons in the cortex are completely disorganized and lack lamination. In the center of the specimen, note the relatively sparse area corresponding to fused molecular layers (fused sulcus) (Nissl, magnification ×25).
become the cerebral hemispheres. These vesicles, which have uniformly thin walls, are connected in the midline by the lamina terminalis. On the subependymal aspect of these vesicles, layers of tightly packed immature pluripotent cells develop (the germinal matrix). The germinal matrix is separated from the pia mater by a superficial acellular zone called the marginal layer. The cells within the germinal matrix give origin to neuroblasts that migrate outwardly to rest eventually in the cortex. This migration begins at approximately 7 weeks of gestation and is completed between 24 and 40 weeks of gestation. Neurons, which will form the cortex, migrate along radial glia to their final destination. The radial cells are initially pseudostratified bipolar immature cells originating from primitive neuroepithelium. The processes of the radial glia, glial fibrillary acidic protein (GFAP), are vimentin positive and extend from the walls of the ventricles to the pia mater. These structures, known as radial glial fibers, are essential because they provide a scaffold on which the young neurons migrate outwardly. Neuronal migration is fed by active proliferation of cells from the germinal matrix. Neuronal migration occurs in waves. The highly populated cortex is separated from the germinal matrix by the intermediate layer, which contains concentric waves and parallel roles of migrating neurons. This intermediate layer progressively increases in size, loses all neurons, and eventually becomes the white matter. Neuronal migration occurs in an “inside out” sequence; that is, the cells of the deepest cortical layer (layer 6) migrate early, followed by cells of layers 5, 4, 3, and 2. Cells that eventually rest in layer 1 (the molecular layer) are an exception to this rule, arriving first at their final superficial cortical destination. Neuroblast formation stops at about 100 days of gestation but migration continues. The germinal matrix involutes completely by the end of the first year of life. A remnant of the germinal matrix can be seen in premature and some term newborns at the level at which the caudate nuclei and thalami are close together (the so-called caudothalamic groove or notch).

A unique feature of the human neocortex is the presence of a temporary superficial granular layer under the pia. Although this feature disappears by 27 to 30 weeks of gestation, areas of retained superficial granular layers can normally be found in the cortex of the temporal lobes and basal cortex of the frontal lobes throughout life. All cortical layers undergo special organization, establishing synaptic contacts with local and distant neurons; these contacts contribute to the normal horizontal and columnar stratification of the layers.

Inhibition of neuronal migration or organization can result in a dysplastic cortex. Dysplastic cortex occurs as a result of a destructive, toxic metabolic event, or of chromosomal deletion anomalies. Polymicrogyria also results from ischemic insults to the developing brain as seen in cases of schizencephaly. Polymicrogyria has been reported to occur at the periphery of porencephalies, presumably because of prenatal infarcts (3). Also, the location of a polymicrogyric cortex often corresponds to well-defined arterial territories such as the middle cerebral distribution (4). Prenatal infection with cytomegalovirus results in meningitis, encephalitis, and ependymitis, and affects the regions of the developing brain with greater cellular proliferation, such as the germinal matrix. Additionally, cytomegalovirus can damage either the radial glial fibers, resulting in abnormal migration, or the established molecular layer, resulting in cortical disorganization. In patients with confirmed prenatal infection with cytomegalovirus, the brain-neighboring regions of polymicrogyria can contain viral inclusions, foci of necrosis, calcifications, heterotopias, and infarctions (3). Therefore, several simultaneously occurring mechanisms, including direct cell loss, loss of integrity at the pial-glial border, hypoxia-ischemia, and other local vascular insults mediated through endothelial damage at the capillary level might play a role in the genesis of polymicrogyria (3). Polymicrogyria has been reported in monozygotic twin recipients and donors of twin-twin transfusions; it was thought to have resulted from blood pressure instability leading to hypoxia-ischemia (5, 6). Inhibition of neuronal chemotaxis may also lead to polymicrogyria (2). Chromosomal abnormalities have been implicated, as in the autosomal recessively inherited bilateral perisylvian syndrome (7).
It is agreed that polymicrogyria most likely results from insults to the developing brain in the late migrational period or after neuronal migration has stopped. The incidence of polymicrogyria is unknown but most patients with polymicrogyria have seizures and are mentally disabled. Histologically, there are several schema that attempt to classify polymicrogyria. Brain injury occurring during the early second trimester of pregnancy (12 to 17 weeks) has been associated with unlayered polymicrogyria; injury occurring later (18 to 24 weeks of gestation) may result in layered polymicrogyria. Norman et al (3) subdivide the above histologic classification as follows: unlayered polymicrogyria can have (a) unlayered cortex, in which a molecular layer is present with a single band of unlayered neurons, resulting in an appearance of looping back and forth, or (b) poorly laminated cortex, in which four individual layers are not distinctly evident; layered polymicrogyria can have (a) four-layered cortex, in which a molecular layer is present, and there is a second layer of un laminated neurons arranged in a sinusuous band with two underlying layers of horizontal, un laminated neurons, and the outermost of these two layers, layer 3, is cell poor; or (b) parallel four-layered cortex, in which there are the same four layers as above, but all are horizontal and parallel each other.

What is clear from the above schema is that there are two types of polymicrogyria, one in which there is no neuronal organization (as in the case here shown) and another in which the cortex is laminated but contains only four layers instead of the normal six. Injury during the postmigrational period typically leads to the classic four-layered cortex with associated laminar necrosis. The basic cytoarchitectonic abnormality is that of ischemic laminar necrosis predominating in layer 5, resulting in a cell-sparse layer. Superficial to this, layers 4, 3, and 2 are normal. It is important to remember that, although the classic description of polymicrogyria is of a four-layered cortex, each case is unique; the appearance may vary from place to place even in the same patient (3).

The clinical presentation of patients with polymicrogyria is variable and depends on the severity of involvement and its location. Most patients present with seizures, usually focal motor, and developmental delay. More than 80% of patients with cortical dysplasias have seizures. (A surgical resection of cortical dysplasias can be beneficial in alleviating or diminishing seizures.) This high incidence of seizures is probably attributable to the presence of lesions in cortical layer 5 (which is a source of epilepsy) and in layer 4, which normally inhibits input onto layer 5 (1). Diffuse polymicrogyria results in microcephaly, hypotonia, and infantile seizures with marked developmental delay. This constellation of features can also be caused by congenital cytomegalovirus infection. Patients with large cortical dysplasias can also have congenital hemiplegia contralateral to the abnormal cortex. In the most severe form of cortical dysplasia, agyria, microcephaly, decerebrated posture, and severe motor retardation are typical (8). Patients with the syndrome of bilateral perisylvian cortical dysplasia present with pseudobulbar palsy, epilepsy, and bilateral motor dysfunction. Rarely, patients with polymicrogyria (even those with extensive dysplasias) maintain near-normal cognitive abilities.

MR imaging is the method of choice for the evaluation of patients with suspected cortical dysplasias. With MR imaging, neuronal migration disorders may be classified as (a) focal, including polymicrogyria and unclassifiable cortical dysplasias, schizencephaly (always associated with dysplastic cortex of the polymicrogyric type), and macrogyria; (b) hemispheric, including hemimegalencephaly and megalencephaly; or (c) diffuse, including bilateral perisylvian dysplasia (polymicrogyria), band heterotopias, lissencephaly-pachygyria complex, and subependymal heterotopias.

Based on the above, polymicrogyria may be a focal or a diffuse process. On MR studies, polymicrogyria is seen as thickened cortex with shallow sulci. Although this appearance is similar to that of pachygyria, in polymicrogyria the width of cortex averages 5 to 7 mm, compared with greater than 8 mm in pachygyria. The outer surface of the dysplastic cortex can be bumpy or smooth, and is occasionally normal in appearance. There may be focal enlargement of the overlying
subarachnoid space and associated underlying parenchymal atrophy.

Although traditionally it has been accepted that polymicrogyria has the appearance of pachygyria on MR studies, this observation is probably related to the fact that initial descriptions were based on thick sections (5 mm or larger), which do not have the spatial resolution to resolve the characteristics of the dysplastic cortex. Polymicrogyria can be clearly appreciated on MR images with thin (1.0- to 1.5-mm-thick) sections and three-dimensional heavily T1-weighted or gradient-echo images (2, 4). One advantage of the latter technique is that multiplanar reforma-
tion is readily achieved and aids in the con-
firmation of dysplastic cortex. In polymicro-
gyria, the superficial cortex may have a
“bumpy” appearance and its inner surface (at
the gray–white matter interface) a corrugated
appearance. On MR imaging, the dysplastic
cortex is typically isointense to normal cor-
tex. Although polymicrogyria can involve any
part of the brain, the region of the sylvian
fissure is most commonly affected (Fig 2).
This observation and the fact that the lips of
schizencephalies are lined by dysplastic cor-
tex have erroneously led some authors to la-
bel some polymicrogyrias as “schizence-
cephaly type I” (9).

Generally, polymicrogyria does not extend
into the ventricle (as schizencephaly does)
and is separated from it by a band of white
matter. In most perisylvian polymicrogyrias,
the fissure is deep and extends farther back
than normal. Calcifications in zones of corti-
cal dysplasias are found in fewer than 5% of
cases (2). Associated anomalous venous
drainage is a relatively common finding.
Anomalous veins are more common when
there is an infolding of dysplastic cortex and
should not be confused with a true arterio-
venous malformation. These anomalous
veins are probably caused by lack of conden-
sation of the cortical veins. The term uncon-
densed cortical veins refers to persistence of
the tributaries of the embryonic dural plexus,
which will later coalesce to form the normal
superficial cortical veins and dural sinuses. If

![Fig 2. Deep cleft (sylvian fissure) related to polymicro-
gyria. Lateral view of fixed brain shows deep right sylvian
fissure, which extends abnormally superiorly and posteriorly.
Note the abnormal course of the sylvian branches of the middle
cerebral artery caused by lack of temporal and parietal
opercula. Cortical veins are not condensed at this level. These
findings are similar to those shown in Figure 1B. Along the
sides of the abnormal sylvian fissure, there are no normal sulci.

![Fig 3. Diffuse polymicrogyria.](A) Axial T2-weighted MR image
(4000/90/1) in a newborn with diffuse polymicrogyria shows incom-
plete sulcation throughout the brain, multiple areas of thick cortex (par-
cularly in the right hemisphere), and a close-lip schizencephaly (ar-
rowheads) involving the left occipi-
tal region. Note slightly corrugated
appearance (small arrows) in the inner border of the polymicrogyric
cortex.

B, Fixed brain in a different case of diffuse polymicrogyria shows
thickened cortex and lack of sulca-
tion.
any doubt exists, MR angiography usually confirms the diagnosis by showing lack of arterial feeders. Large areas of dysplastic cortex occasionally engulf portions of the subarachnoid space that on MR imaging can simulate cysts within a mass. If these dysplasias are not recognized as such and biopsy is done, the pathologist might misinterpret them as ganglion cell tumors. Proton MR spectroscopy can play a role in these cases by establishing that metabolites (namely choline, creatine, and N-acetylaspartate) are in concentrations very similar to those of normal brain (10).

The white matter underlying polymicrogyria can also be abnormal. As many as 20% of patients show hyperintensity in underlying white matter on T2-weighted images (2). This hyperintensity can be present at birth or develop with age. It can be secondary to gliosis, probably caused by ischemia or poor, delayed, or absent myelination. Additionally, the gray–white matter interface can be indistinct by MR imaging in cases of cortical dysplasias. On MR imaging, diffuse polymicrogyria appears very similar to pachygyria (Fig 3).

Positron emission tomography and single-photon emission computed tomography (SPECT) have been used to detect abnormal local metabolism and perfusion related to the presence of cortical dysplasias. Positron emission tomography has been shown to be sensitive in locating focal areas of cortical dysplasia, heterotopias, and other migration abnormalities corresponding to surface electrographic location of epileptogenic regions (11). SPECT can help identify cortical dysplasias by demonstrating hypoperfusion during the interictal phase and hyperperfusion during seizures (12).

References