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Correlation of Prenatal Events with the Development of Polymicrogyria

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Summary: We report two cases of polymicrogyria in which maternal insults were well documented during the first half of the second trimester of pregnancy. The clinical histories, MR studies, and, in one patient, autopsy results were carefully reviewed, and the timing and nature of the injuries correlated with known developmental events at the time of the injury. Our results support the theory that polymicrogyria results from injury to, or disruption of normal cellular interactions at, the external limiting membrane (the "glial-pial barrier").

Index terms: Migration anomalies; Fetus, growth and development; Brain, abnormalities and anomalies

With the advent of magnetic resonance (MR) imaging, disorders of neuronal migration, once thought to be rare brain anomalies, have been shown to be rather common causes of neurologic disorders (1–4). As these disorders are now commonly diagnosed and sometimes amenable to surgical therapy (5, 6), a great deal of effort has gone into the investigation of the process of neuronal migration (7–9). The investigations have, in turn, spawned a number of theories regarding the causes and mechanisms of the migration arrest and disorganization of the resultant cerebral cortex (2, 10–15). Despite this research, few cases are reported that link prenatal incidents with anomalous neuronal migration. In this communication, we report two cases of neuronal migration anomalies, one with pathologically proved polymicrogyria and one with classic MR features of polymicrogyria, that have well-documented prenatal events as their presumed cause. Both patients were reported previously (1).

Case Reports

Case 1

A boy was born to a gravida 2, para 1 mother after a pregnancy complicated only by maternal ingestion of a combination of caffeine and ergotamine tartrate for headache at 16 to 18 gestational weeks. The birth was uneventful except for some late decelerations on the external fetal monitor. Apgar score was 6/9 at 1 and 5 minutes. Head circumference, weight, and length were at the 25th, 50th, and 50th percentiles, respectively. The postnatal course was unremarkable until age 12 months, when some delay in gross motor development was noted. The patient did not walk until 23 months. Speech was also delayed. He attended a special school, and was noted to have severe behavioral problems. Seizures developed at age 7 years and consisted of absence episodes initially, with subsequent atonic drop attacks.

Examination was difficult because of the child's short attention span and difficulty in following commands. He was noted to have mild hyperreflexia and poor gross and fine motor control. A brisk jaw jerk was present. Speech was slow and stammering.

Electroencephalography (interictal) showed synchronous bilateral bursts of spike and slow waves in the central regions of the head at a frequency of 2.5 to 3 Hz. Bilateral independent sharp and slow wave complexes were superimposed in the posterior frontal regions.

MR at age 11 years (Fig 1) showed irregular infoldings of thickened cerebral cortex that were continuous with the posterior aspects of the sylvian fissures bilaterally in the frontoparietal regions. This MR appearance is classic for bilateral opercular polymicrogyria (1, 3, 4, 16, 17). White matter was diminished around the atria and occipital horns of the lateral ventricles, resulting in dilatation of those portions of the ventricles, diminished distance between the ventricular surface and the depths of the cortical gyri, and thinning of the posterior body and splenium of the corpus

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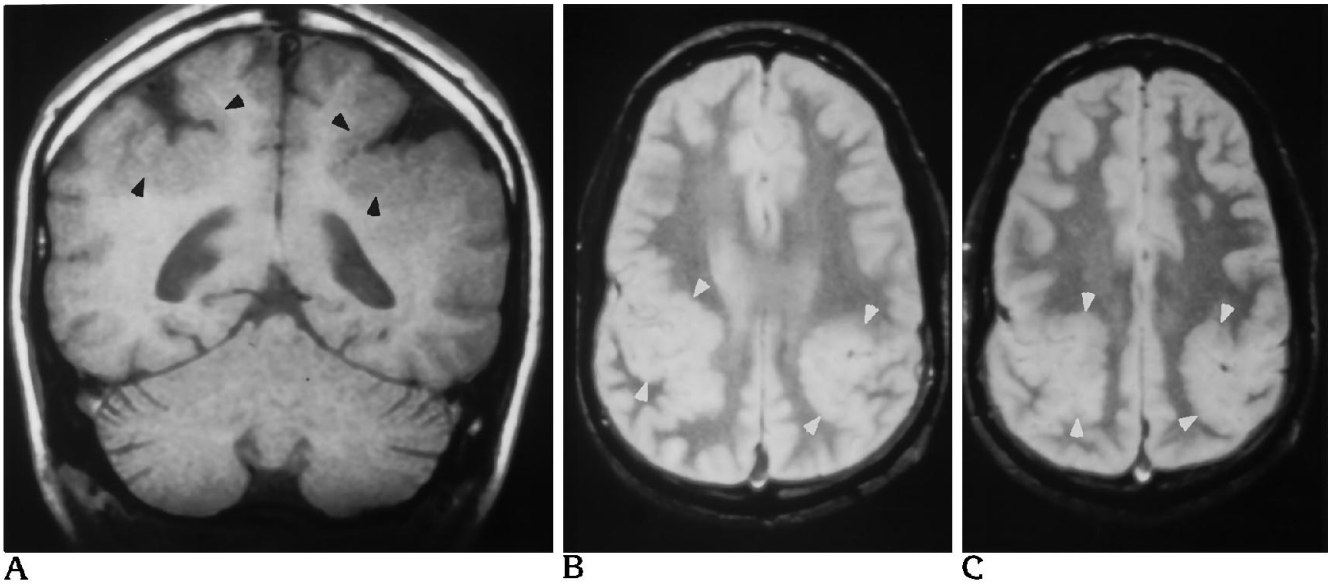

Fig 1. Case 1.

A, Coronal T1-weighted MR image shows bilateral infoldings of cerebral cortex (*arrows*) in the posterior frontal/parietal region. The involved cortex is abnormally thick and has irregular inner and outer surfaces.

B and *C*, Axial T2-weighted images show the irregular contour (*arrows*) of the thick cortical infolding at the gray matter–white matter junction ([from Barkovich and Kjos [1]).

callosum. Myelination was appropriate for age. The posterior fossa, globes, and orbits were normal.

Case 2

A girl was born at full term to a 34-year-old gravida 3, para 2 or 3 mother and a 41-year-old father. The pregnancy was notable for 1- to 2-day exposure to strong varnish fumes at 16 to 17 weeks' gestation. The birth was uneventful. Apgar score was 5/7 at 1 and 5 minutes. At birth, head circumference was 32 cm (5th percentile), length was 45 cm (5th to 10th percentile), and weight was 3052 g (25th to 50th percentile). The parents noted problems in the newborn period. Although the child fed well, she awoke several times nightly with choking or regurgitation. At 6 weeks, eye rolling and arching of the back began. At 14 weeks, episodes of bilious vomiting followed by extreme lethargy occurred. Examination at that time showed a head circumference of 37 cm (<2nd percentile). Fair head control was noted along with symmetric grasps and normal suck, root, and Moro responses. Reflexes were normal; clonus was not elicited. Electroencephalography showed a 3- to 4-Hz background with superimposed sharp waves arising independently from both hemispheres, left greater than right.

Examination at age 7 months showed an obviously microcephalic infant with head circumference of 39.2 cm (<2nd percentile), length of 65 cm (10th to 25th percentile), and weight of 7.8 kg (25th percentile). The examination was remarkable for episodes of gagging, stiffening, and breath-holding. The anterior fontanelle was not palpable. Pupils were reactive, but eyes were disconjugate without tracking or fixation. Tone was spastic in neck, limbs, and trunk; hands were clenched and limbs extended. Reflexes were hyperactive and toes extensor bilaterally. Sensation was grossly normal. Laboratory screening included complete blood count; glucose; ammonia; liver function studies; blood pH; urinary amino acids; and titers for toxoplasmosis, rubella, cytomegalovirus, herpes viruses, syphilis, and other viruses; all were normal.

MR at age 4 months (Fig 2A and B) showed a diffusely abnormal brain with a slightly thickened cerebral cortex, irregular cerebral gyral pattern, and diminished cerebral white matter. Myelination was roughly appropriate for age, although the optimum sequences for assessing myelination were not performed. The posterior fossa, orbits, and globes were normal.

Over the remainder of the clinical course, the patient gained few, if any, milestones. She could open and close her hands and supported her head against gravity, but this was judged a consequence of spasticity. Seizures persisted, gradually including more obvious motor manifestations. Although no serious acute medical illnesses developed, irritability, crying fits, and choking spells continued. No benefit was noted from triazolam, clonazepam, or valproic acid. At age 10 months, she had an ear infection, lost her appetite, had fluctuating temperatures up to 40.6°C, and died after 1 week. At autopsy, the cause of death was thought to be respiratory failure secondary to bilateral lobar pneumonia. The brain weighed 400 g (normal for age, 800 g). Leptomeninges were clear and transparent. The brain surface showed numerous abnormal small gyri diffusely over the cerebrum surface (Fig 2C–F). Histologic examination showed a disorganized cortex with-

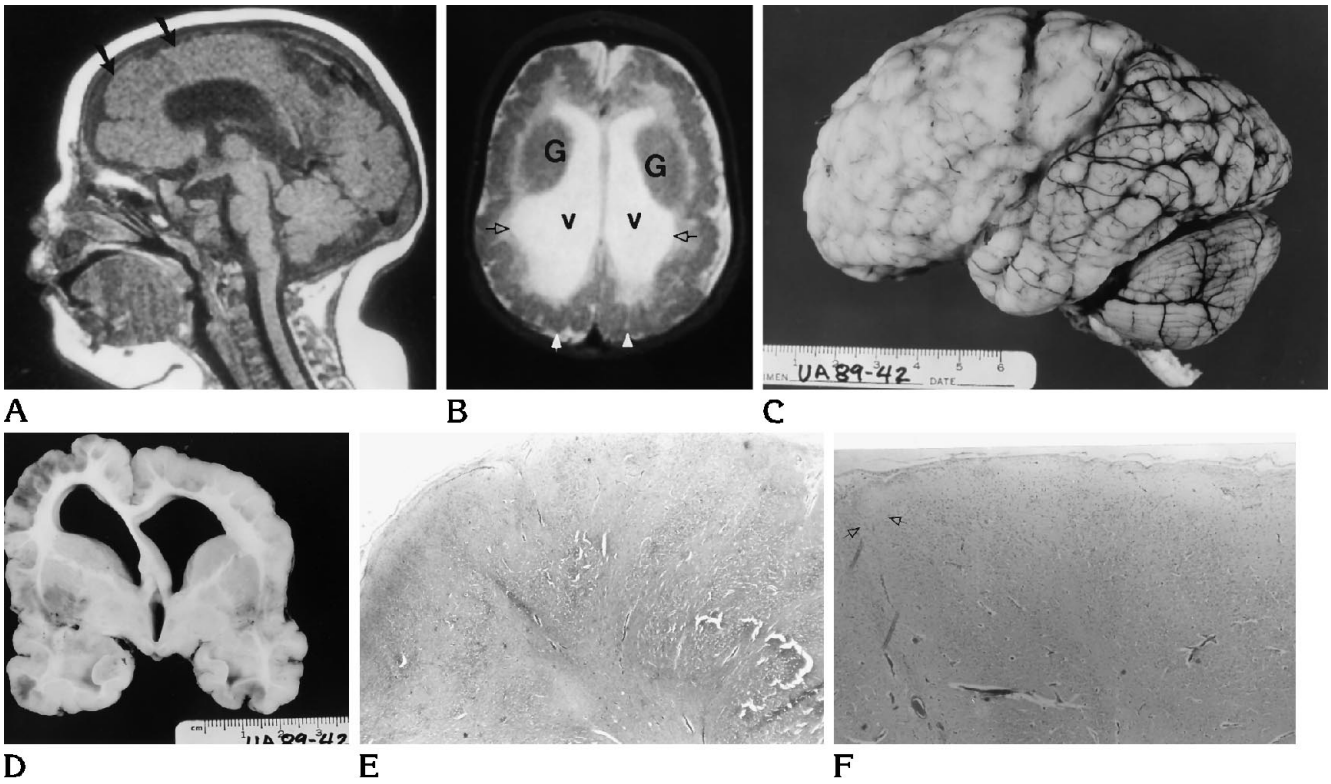

Fig 2. Case 2.

A, Sagittal T1-weighted MR image at age 4 months shows decreased cerebral convolutions, particularly in the frontal lobes (*arrows*).

B, Axial T2-weighted image shows a very abnormal gyral pattern. In the frontal lobes, the cerebral cortex has irregular, "bumpy" inner and outer surfaces. A few somewhat normal-looking gyri are present in the occipital region (*solid arrows*). A diminished volume of white matter separates the basal ganglia (*G*) from the cortex. The lateral ventricles (*v*) are enlarged, with focal expansion of the posterior bodies (*open arrows*).

C, Photograph of the whole brain after removal from skull at autopsy (compare with Figure 1A). The frontal and temporal lobes appear most severely affected, but histologic examination showed the parietal and occipital lobes to be abnormal as well (from Barkovich and Kjos [1]).

D, Coronal brain slice at autopsy shows a very abnormal cortical gyral pattern, with thickened cortex, bumpy outer cortical surface, and decreased interdigitation of the white matter into the gyri. The lateral ventricles are enlarged, and a diminished quantity of white matter separates the ventricles from the cortex.

E, Photomicrograph of frontal cortex shows features of polymicrogyria; gyri are small, sulci are shallow, and adjacent gyri are fused (Nissl stain, magnification ×10).

F, Photomicrograph of temporal cortex shows apparent fusion of molecular layers (*arrows*). Note the lack of cortical lamination and the absence of a cell-sparse layer, establishing this as unlayered polymicrogyria (Nissl stain, magnification ×25).

out normal cortical layering and with nearly random orientation of neurons. A "cell-sparse layer" was not identified.

Discussion

Polymicrogyria refers to an abnormal macroscopic and microscopic appearance of the cerebral cortex. Grossly, the surface of the brain is characterized by too many abnormally small convolutions. In some patients, the small gyri are separated by shallow sulci. In others, the gyri are wider, but with minute indentations, whereas still others have small, irregular gyri without intervening sulci or with sulci obliterated and bridged by fusion of the molecular layers (18, 19).

Although a spectrum of histologic findings have been described in cases of polymicrogyria, two major histologic variants have been identified. The best described variant is the so-called "layered" polymicrogyria, which is characterized by a cell-sparse zone of laminar necrosis that predominates in cortical layer V (20). Peripheral to this band of necrosis, layers II, III, and IV appear normal on light microscopy. The zone of necrosis enhances the growth difference between the central and peripheral cortical layers; this differential is theoretically the

cause of the excessive cortical folding (21). The other common histologic appearance of polymicrogyria is that of "unlayered" polymicrogyria, in which no cell-sparse layer is present and the superficial cortical layers appear very disorganized (22).

Most authors suggest that many, if not most, cases of polymicrogyria result from ischemia (14, 23, 24). This concept is supported by the findings of Innocenti (25), who has shown in an experimental model that ibotenate, an excitotoxic amino acid, induces cortical laminar necrosis. This effect presumably results from a relatively increased concentration of excitotoxic amino acid receptors, such as *N*-methyl-D-aspartate receptors, in specific cortical laminae as compared with others. Activation of the excitotoxic amino acid receptors results in depolarization of the neuronal membranes, loss of the magnesium ion blocking calcium channels, intracellular influx of calcium, and a series of subsequent steps leading to cell death. Excitotoxic amino acids are proposed to be an important factor in ischemic brain damage (26).

Some authors (22, 23) have suggested that polymicrogyria results from a postmigrational laminar cortical necrosis. To support this theory, they point out the normal histologic appearance of the superficial cortical layers peripheral to the cell-sparse zone. However, Humphreys et al (12) and Suzuki and Choi (14) have used immunocytochemical studies to demonstrate regional disturbances of neuronal architecture in superficial cortical layers of polymicrogyria that appeared normal on Nissl stains. Moreover, Humphreys et al have demonstrated that neurons can migrate through a laminar necrosis, and Marin-Padilla (personal communication) has shown a possible late renewal of migration of superficial cortical layers. Finally, Suzuki and Choi have shown that, although superficial cortical injury to rats on the day of birth or 1 day after birth (an age at which neurons are still migrating) will have a resultant injury identical to layered polymicrogyria, an identical injury at age 10 days (after cessation of neuronal migration) will result in a typical adult-type infarct. Thus, most evidence now supports the theory that layered polymicrogyria results from a cortical injury before the termination of cell migration.

In unlayered polymicrogyria, no cell-sparse layer is present, leading some authors to speculate that the unlayered form is the result of localized vascular occlusion and deeper brain infarction (22). This proposal is supported by the observations of McBride and Kemper (27), who found unlayered polymicrogyria in the central and, presumably, more severely affected portion of a large microgyric region. The more peripheral microgyric regions had a typical four-layered appearance.

A few case reports have been published that give added clues to the timing of injuries that result in polymicrogyria in humans. Two cases of carbon monoxide inhalation by pregnant mothers between 20 and 24 weeks (28, 29) resulted in layered polymicrogyria. Two cases of parabiotic twins have been reported in which an accident resulted in the death of one twin and bilateral unlayered polymicrogyria in the other (30, 31). Analysis of the dead twins allowed the injury to be dated to between 13 and 16 weeks.

The cases reported herein are further evidence that polymicrogyria results from an injury to the brain during the early to middle portions of the second trimester. Although one cannot unequivocally establish in either case that the maternal insult was the cause of the fetal malformation, the timing and nature of the insults strongly support them as playing a major role in the development of fetal microgyria. Moreover, case 1 provides further evidence that in utero ischemia results in injury that ultimately causes polymicrogyria. The combination of caffeine and ergotamine tartrate, a potent smooth-muscle stimulator, causes marked uterine contraction and almost certainly would result in significantly decreased blood flow to the brain of the fetus. Additionally, ergotamine will cross the placenta in small quantities (32) and has some specific vasoconstrictive effects on cerebral vasculature (33). Moreover, the symmetric location of the lesions in the posterior frontal and parietal lobes (the most common location for dysplastic cortex [1, 2]) may be an intervascular boundary zone at mid–second trimester, when both the middle and posterior cerebral arteries are fully formed (34).

The mechanism of brain injury in case 2 is less straightforward. The ingredients in varnish include toluene and other, usually nonaromatic, hydrocarbons. Although toluene has not been directly implicated as a cause of neuronal migration anomalies, it has been shown to cause variable growth deficiency, minor craniofacial and limb anomalies, central nervous system dysfunction, and microcephaly in human (35)

and animal (36) offspring of parental toluene abusers. Moreover, the affinity of toluene for lipid-rich tissue results in neurotoxicity in chronic abusers, manifested by cerebellar degeneration and cortical atrophy (37). Nonaromatic hydrocarbons have similarly been implicated in central nervous system anomalies (38–40), although, once again, anomalies of neuronal migration have not been specifically identified. However, it is well known that toluene and hydrocarbons gain ready access to the maternal blood from the lungs and, as small hydrocarbons, have no difficulty crossing the placenta into the fetal blood and exiting from the fetal blood vessels into the developing fetal central nervous system. Once in the central nervous system, one can easily envision that hydrocarbons could interact with chemical moieties in the developing brain that normally guide the neurons to their final destinations along the radial glial cells. Alternatively, the hydrocarbons could interact with chemical markers on cell surfaces or in the intracellular space that initiate dissociation of the neuron from the radial glial cell or the formation of synapses with other cells in the milieu of the developing cortex. Finally, these chemicals could impair the formation of, or the normal interaction of the migrating neurons or the radial glial fibers with, the so-called pial-glial barrier (14); these interactions appear to be very important in cortical organization (14, 41, 42). Any of these chemical interactions could, theoretically, result in the disorganized cortex seen in this and many other cases of polymicrogyria. The actual mechanism awaits further experiments.

To summarize, we have presented further evidence that polymicrogyria results from an injury to the fetal brain during the early to middle second trimester. Furthermore, our data suggest that both fetal ischemia and maternal hydrocarbon exposure can result in cerebral microgyria.

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