

Bilateral Frontal Polymicrogyria – An Autopsy Case Report –

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Bilateral frontal polymicrogyria is a recently recognized syndrome characterized by symmetric polymicrogyria of both frontal lobes that presents with delayed motor and language development, spastic quadriparesis, and variable mental retardation. However, the postmortem findings of this syndrome are not fully elaborated. Here we describe an autopsy case of bilateral frontal polymicrogyria in a male fetus delivered at 22 weeks gestation due to extensive chorioamnionitis. The microscopic findings included a thinned cortical plate with fair neuronal maturation. There were no signs of neuronal damage and the white matter was unremarkable.

Key Words: Frontal lobe; Malformations of cortical development; Chorioamnionitis; Neuronal migration disorders

Polymicrogyria, which is characterized by an excessive number of small gyri with abnormal cortical lamination, is a common malformation of cerebral cortical development. The incidence of polymicrogyria is unknown. The diagnosis of polymicrogyria is being made more frequently due to advances in magnetic resonance imaging.¹

Several region-specific bilateral polymicrogyria syndromes have been described. These include bilateral frontal polymicrogyria, bilateral frontoparietal polymicrogyria, bilateral perisylvian polymicrogyria, bilateral parasagittal parieto-occipital polymicrogyria, and bilateral generalized polymicrogyria. Among these syndromes, bilateral frontal polymicrogyria is a rare, recently described syndrome. It is characterized by symmetric polymicrogyria of both frontal lobes that presents with developmental delays, mild spastic quadriparesis, impaired language development, mental retardation, and epilepsy.² Only 15 cases have been reported in patients between the ages of 10 months and 32 years. There were no histological examinations performed on any of these patients.²⁻⁴

We describe an autopsy case of bilateral frontal polymicrogyria in a male fetus delivered at 22 weeks gestation due to chorioamnionitis. Most reported cases of this syndrome are based on magnetic resonance imaging in children and adults. Because of this, histological changes in the fetus were expected to be seen as this malformation is a congenital anomaly.

CASE REPORT

A 25-year-old primigravid woman at 22 weeks gestation was transferred to our hospital due to severe chorioamnionitis with premature rupture of the amniotic membrane and anhydramnios. The amniotic membrane had ruptured two weeks prior and she had been admitted to another hospital where she was managed with antibiotic therapy. At our hospital, she delivered a dead male fetus. At autopsy, the fetus weighed 523 g. It measured 21.5 cm in crown-rump length and 29.5 cm in crown-heel length. The head circumference was 19 cm, chest circum-

ference was 17 cm, and abdominal circumference 17.5 cm. There were no external gross abnormalities. The body measurements and organ weights were appropriate for a Korean fetus at 22 weeks gestation.⁵ The brain weighed 94 g and showed bilateral symmetric distribution of polymicrogyria in the frontal lobes, sparing the prefrontal area and the base of the frontal lobe (Fig. 1). The sylvian fissures, calcarine fissures, parieto-occipital fissures, and callosal sulcus were seen. Microscopically, the cortical plate and cortical neurons of the polymicrogyria were thin and scarce

compared to a normal cortex of the same gestational age. There were no abnormalities in the maturation of the cortical neurons, which showed vague lamination. The fissural area of the polymicrogyria was the thinnest zone of the cortical plate (Fig. 2). We did not observe neuronal apoptosis, necrosis, dysmorphic neurons, balloon cells, or giant neurons. The white matter showed normal cellularity of the pre-myelin glial cells. No focal necrosis or cellular clusters were noted. The ventricular surface and leptomeninges showed no inflammatory changes. The cere-

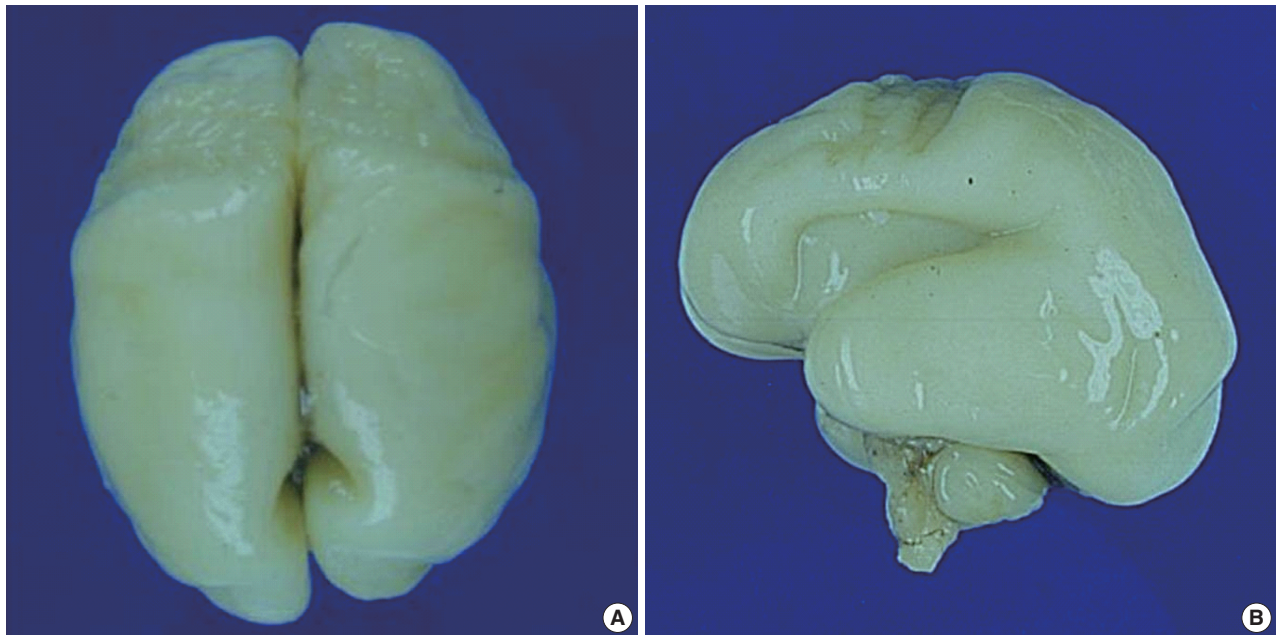


Fig. 1. A superior view of the brain (A) shows bilateral symmetric distribution of polymicrogyria in the frontal lobes. The polymicrogyria abruptly end at the pre-central gyrus. A lateral view of the brain (B) shows frontal polymicrogyria, sparing of the prefrontal area, and the base of the frontal lobe. The sylvian fissure is well developed.

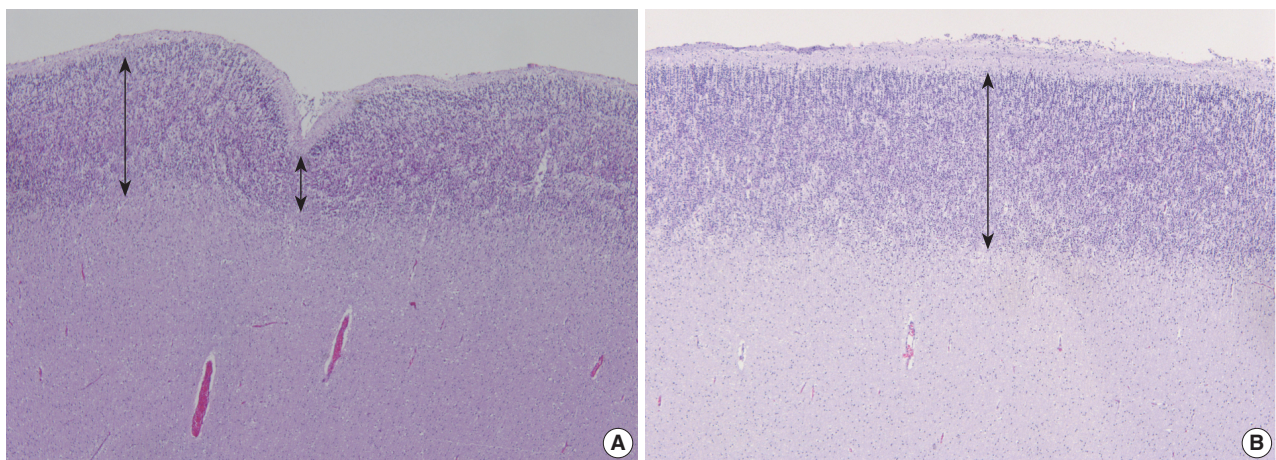


Fig. 2. Microscopically, the cortical plate (arrows) in polymicrogyria (A) is thinner than that found in a normal cortex (B). However, the cellularity and maturation of the cortical neurons are similar.

bellum and brain stem structures showed no abnormalities. The placenta measured 14×12.5×2 cm, and weighed 155 g. There was a diffuse infiltration of neutrophils throughout the chorion, amnion, and chorionic plate vessels. However, the umbilical cord did not have evidence of phlebitis, arteritis, or inflammation of the Wharton's jelly. The chorionic villi showed normal maturation and no inflammatory changes. A chromosomal study of the fetal tissue revealed that the fetus was 46,XY.

DISCUSSION

Among the syndromes involving bilateral symmetric polymicrogyria, bilateral perisylvian polymicrogyria was the first described and is the most common.¹ Its prevalence, like that of the other syndromes, remains unknown. Four cases of Korean children with congenital bilateral perisylvian syndrome have been reported.⁶ Clinical manifestations appear to correlate with the involved cortical regions. Cases of bilateral polymicrogyria appear to be becoming more common due to the increased use of magnetic resonance imaging and increasingly meticulous clinical evaluations for patients with epilepsy, neurological disorders, and developmental delays. Polymicrogyria may result from both genetic and environmental factors. It can occur as an isolated finding, or as part of a syndrome with multisystem involvement. Bilateral symmetric polymicrogyria is considered to be a genetic disorder based on patterns of familial occurrence and genetic analysis.¹

Bilateral frontal polymicrogyria was first described in 13 patients in 2000.² Only two additional cases have been reported since then. One case was associated with Ehlers-Danlos syndrome. The other case was associated with Turner mosaicism.^{3,4} Clinical features such as early developmental delay, mild spastic quadriplegia, impaired language, and variable mental retardation, manifest due to the extensive involvement of the frontal lobes, including the motor cortex. Epilepsy was present in six of the 15 patients.²⁻⁴ Early detection was frequent during investigations for delayed motor development. This explains the relatively low prevalence of epilepsy found among these cases. The diagnoses were made between the ages of 10 months and 32 years. Only three of the 15 patients were over eight years in age at the time of diagnosis.²⁻⁴ This is the first autopsy report of a case of bilateral frontal polymicrogyria. It was an incidental finding from an aborted fetus that was diagnosed at 22 weeks of gestation, before the development of any symptoms.

Bilateral frontal polymicrogyria is thought to be inherited in

an autosomal recessive manner. This is based on the sporadic occurrence of the syndrome in all 13 of the patients. Two patients came from families in which the parents were consanguineous.² Thirteen patients had a normal karyotype, but one patient had Turner mosaicism.^{2,4} The karyotype of our case turned out to be normal, but the family history was not thoroughly investigated.

Microscopically, two types of polymicrogyria have been described. The first is unlayered and the second is four-layered. This is in contrast to normal gyria, which are six layered. There is no laminar organization in an unlayered cortex. This reflects an early disruption of normal neuronal migration which occurs between the 10th and 18th weeks of gestation. Four-layered polymicrogyria is thought to arise from a late disruption of neuronal migration or cortical disorganization which occurs between the 20th and 24th weeks of gestation. It consists of a first molecular layer, a second cellular layer, a third layer which is devoid of neurons, and a fourth cellular layer.^{1,2} There was no disruption of neuronal migration or cortical organization of the polymicrogyric cortex in the present case. However, the cortical thickness and cortical neuronal cellularity of the polymicrogyria were thinner and scarcer compared to those of a normal cortex. The polymicrogyric cortex of the present case showed some lamination. This means that it was not the unlayered type. A normal cortex does not show six distinct layers at 22 weeks gestation. Consequently, it is hard to determine if the cortex is four-layered until the cortical organization has progressed to a more developed state.

Polymicrogyria that results from hypoxic-ischemic insults is often limited to the area fed by a main artery, or the area between two major arterial territories.² We excluded an ischemic cause in this case because there was no suspicious history or pathologic findings of hypoxic-ischemic damage. Furthermore, extensive bilateral frontal involvement is not compatible with any known vascular topography.²

The association between chorioamnionitis and polymicrogyria was suggested by Toti *et al.*⁷ Toti *et al.*⁷ performed gross examinations of normal brain samples from 32 fetuses that were spontaneously aborted due to chorioamnionitis only without clinical evidence of polymicrogyria at 15-26 weeks gestation. They reported various cerebral cortical histological alterations, including undulation of the cortical ribbon, untimely cortical folding, molecular layer fusion, and neuronal loss and/or necrosis in 78% of the fetuses. They concluded that chorioamnionitis may disturb cortical morphogenesis and play a role in the development of polymicrogyria in surviving fetuses.⁷ However,

they did not have a clinical polymicrogyric case that was associated with chorioamnionitis, and no subsequent case report followed which supported their conclusion. The bacteria that are responsible for chorioamnionitis are species with low virulence and are generally of vaginal origin, so that the chorioamnionitis may not be a cause of the polymicrogyria. Usually clinical chorioamnionitis is associated with periventricular leukomalacia, intraventricular hemorrhage, and cerebral palsy.⁸ Although the case reported here was associated with chorioamnionitis, we did not observe the periventricular leukomalacia and periventricular hemorrhage or the histologic findings that were described in the normal cortex by Toti *et al.*⁷ We cannot exclude an inflammatory cause, but it is less likely that chorioamnionitis could have lead to bilateral symmetric polymicrogyria of the frontal lobes in this case.

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