J Korean Epilep Soc 4(2) : 83-86, 2000

Normal Cortical Development and Pathologic Features of Malformations of Cortical Development(MCD)

대뇌피질의 정상발달과 대뇌피질기형의 병리소견

Min-Cheol Lee, M.D.
이 민 철

Normal Cortical Development

The human nervous system makes its first appearance as a groove in the ectodermal component of the embryonic disk during the third week after fertilization. The groove becomes deeper and the upper edges gradually unite to produce a neural tube. The anterior part of the neural tube develops into the brain, the posterior part becomes the spinal cord, and motor nerves appear as local outgrowths from both regions. Development progresses rapidly and the brain of the average mature newborn infant weighs about 450 gm, almost one third as much as the adult brain. The hemispheres in early fefal life are smooth until the 5th month. The gyri of the cerebral hemispheres are produced as a result of unequal growth of the gray and white matter. The form and direction of the principal gyri and sulci are outlined during the 4th month, and by the time of birth all of the main ones are present.

The neuroepithelial cells around the lumen of the neural tube, the germinal cells, generate the cells of the mature nervous system. Each distinct set of neuron originates according to a fairly rigid time table. Once young neurons have formed in the ventricular zone, they move away from it and take their final position in two patterns, i.e., "outside-in" and "inside-out". Programmed cell death occurs as a part of normal development. The development of the central nervous system is a continuous process during the embryonic and fetal periods. For a better understanding of congenital anomalies of central nervous system, three major events of normal development, i.e., neurulation (3 to 4 weeks), bran vesicle formation (4 to 7 weeks) and mantle formation (over 8 weeks) should be kept in mind.

The first category of anomalies is neural tube defect. Neural tube defects encompass all the anomalies arise in completion of neurulation. Anencephaly, Arnold-Chiari malformation, encephalocele, cranial meningoceles, and spinal dysraphism are examples of neural tube defect.

The second category of central nervous system anomalies is disorders of brain vesicle formation. Alobar, semilobar and lobar holoprosencephaly examples of failure of brain vesicle formation.

The last category of central nervous system malformation is disorders involving the process of mantle formation. The cerebral mantle is formed through the cellular processes characterized by proliferation, migration and differentiation. In the human, neurons are generated in two bursts, the first from 8 to 10 weeks and next from 12 to 14 weeks. By 16 weeks, most of the neurons have been generated and have started their migration into the cortex. Agyria/pachygyria, heterotopia, polymicrogyria, and cortical dysplasia constitute neuronoglial malformative lesions associated with medically intractable epilepsy.

Pathological Classification of Disorders of Cortical Development(DCD)

1. Categories of DCD

Nearly all malformations of the brain are either pri-

전남대학교 의과대학 병리학교실
Department of Pathology, Chonnam National University Medical School, Kwangju, Korea
교신저자 : 이민철, 501-190 광주광역시 동구 학1동 5
TEL : (062) 220-4300 · FAX : (062) 227-3429
E-mail : mclee@chonnam.ac.kr

Table 1. Developmental cortical malformations

Ⅰ. Malformations due to abnormal neuronal and glial proliferation		
	A. Generalized	B. Focal or multifocal
1. Decreased	Microencephaly	NK
2. Increased	NK	Hemimogalencephaly without cortical dysplasia(CD)
3. Abnormal		
a. neoplastic	NK	DNET Ganglioglioma/ Gangliocytoma
b. non-neoplastic	NK	Tuberous sclerosis(type 1, 2) Focal cortical dysplasia(FCD) Hemimegalencephaly with CD
Ⅱ. Malformations due to abnormal neuronal migration		
A. Generalized		B. Focal or multifocal
1. Lissencephaly : type 1, 2, NOS		1. Focal agyria/pachygyria (partial lissencephaly)
2. Pachygyria		2. Unlayered PMG
3. Unlayered polymicrogyria(PMG)		3. Heterotopia abnormal cortical organization
4. Heterotopia(subependymal, subcortical, subpial)		4. Cortical infoldings (unilateral)
5. Cortical infoldings(symmetric)		5. Excessive single ectopic white matter neurons
Ⅲ. Malformations due to abnormal cortical organization		
A. Generalized		B. Focal or multifocal
1. Polymicrogyria(PMG)		1.PMG 2. Schizencephaly/PMG 3. Focal or multifocal CD 4. Microdysgenesis (MD)
Ⅳ. Developmental cortical malformation, NOS		

NK : not known, CD : cortical dysplasia, DNET : dysembryoplastic neuroepithelial tumor, (Cited from Kuzniecky RI and Barkovich AJ : J Clin Neurophysiol 13 : 468-480, 1996 with modification)

mary disorders of neuroblast migration or involve migration secondarily, and are frequently recognized as a cause of epilepsy in children and adults. Over the past ten years, many terms have been used to identify malformations of cortical development, including neuronal migration disorders (NMD), cortical dysplasia, cortical dysgenesis, and so forth. Recently, the term "malformations of cortical development (MCD)" was suggested because these malformations result form disturbed organogensis and all involve cells forming the cerebral cortex. In addition, a classification based on the embryological, anatomical, and genetic bases of the developmental disorders rather than on the gross pathological, electrophysiological, or clinical presentation. This classification system categorized the major malformations on the basis of three main steps in development: 1) Stem cell proliferation and differentiation, 2) neuronal migration, and 3) cortical organization (Table 1).

2. Neuropathology of cerebral cortical dysplasia

Cortical dysplasia (CD) represents a spectrum of neuropathologic changes reflecting a derangement of the normal process of neocortical development. We have presented 32 patients who underwent cortical resections for intractable seizures and demonstrated the neuropathologic features, which could be explained by a disturbance in the process of neural development in the fetus. It could be characterized by light microscopic features: cortical laminar disorganization, neurons in the molecular layer, subpial remnants of granule cells, remnants of marginal glioneuronal heterotopia, neuronal heterotopia in the white matter, polymicrogyria, neuronal cytomegaly and balloon cell change. Even though cortical dyslamination was the consistent finding of all the cases, the neuronal cytomegaly and balloon cell change were diagnostic hallmarks in the study. The cytomegalic neurons were strongly reactive by silver impregration, and to immunohisochemical markers of neuron such as neurofilament protein (NF, 68 and 200 kDa) and neuron-specific enolase (NSE). The showed hypertrophic endoplasmic reticulum and increased number of mitochondria in their cytoplasm, and incomplete synapses in electron microscopic study. The balloon cells were positively stained by glial fibrillary acidic protein, NSE and vimentin, and were filled with abundant intermediate filaments in their cytoplasm electron microscopically.

The results indicated that both cytomegalic neurons and balloon cells appeared by faulty cell differentiation involving neuroblast in the former, and both neuronal and glial stem cell lines in the latter.

3. Neuronal migration disorder(NMD) : neuropathology and proposal for a grading system

Many diagnostic terms, such as cortical dysplasia, microdysgenesis, cortical dysgenesis, glioneuronal hamartia and NMD, and different grading systems have been used to identify malformations of cortical development caus-

ing medically intractable epilepsy. But the reproducibility of the diagnosis and classification is still difficult secondary to various histopathologic features. We studied 74 patients with NMD who underwent partial lobectomy to define histopathologic criteria and simple grading system. They included some cases of pachygyria, schi-zencephaly, polymicrogyria (PMG), and tuberous sclerosis. Tissue sections evaluated by H & E, Nissl, Bielschowsky, and luxol fast blue stains, immunohistochemistries for neural antigens, and electron microscopy. The cytogenetic study was performed in two PMG cases. The essential findings are abnormal cytologic features of neural cells and/or normal appearing ectopic neurons. The abnormal cells consist of three types; dysplastic neurons, dysplastic astrocytes and ballooned cells which subclassified into four types by immunohistochemical charac- teristics. The two PMG cases show 46, XY, dup(9p) and 47, XY, +19, dup(9p) by karyotypic analysis. From the simplified histopathologic features and cytogenetic study, we propose four grading system (Table 2), and it will be served as an easy accessable communication between the pathologist and clinician.

4. Cytoskeletal changes in cortical dysplasia

Cortical dysplasia is a cause of intractable epilepsy and a candidate for surgical resection to control epileptic attacks. The neuronal cytomegaly and balloon cell change are the diagnostic hallmarks of cortical dysplasia. Little research has been performed about the normal-sized dysplastic neuron which has complex arborizing dendrites and lacks in its polarity. The aim of this study was to define the histopathologic characteristics of the neurons in cortical dysplasia. Twelve cases of cortical dysplasia who underwent partial lobectomy for intractable seizures were selected and immunohistochemical staining for NF-M/H, MAP2, tau, and ubiquitin was performed. The perikarya and dendrites of dysplastic neurons were more intensely labeled with antibodies for the high and medium molecular weight neurofilament proteins (NF-M/H) than normal neurons. Immunoreactivity with the MAP2 antibody expressed mainly within the somatodendritic regions was present in the dysplastic or normal neurons without any significant difference in intensity. The complex arborizing dendrites of dysplastic neurons were easily identified due to pronounced immunoreactivity within the somatodendritic regions. Immunoreactivity with the primary antibody against tau and ubiquitin was present in the normal-looking neurons as well as the dysplastic neurons. This study suggests that the dysplastic neurons in cortical dysplasia are accompanied by changes of cytoskeletal neurofilaments, and the immunohistochemical stains for NF-M/H, MAP2, tau, and ubiquigin are useful to detect them.

Table 2. Histopathologic grades of neuronal migiathion disorder

Grade		Pathologic features
I	a	Four-layered polymicrogyria
	b	Microdysgenesis or heterotopia
II		Small dysplastic neurons and astrocytes
III		Cytomegalic neurons
IV	a	Ballooned cells
	b	Tuber in tuberous sclerosis

5. Dual pathology of hisppocampal sclerosis and neuronal migration disorder in patients with temporal lobe epilepsy

Hippocampal sclerosis (HS) or mesial temporal sclerosis (MTS) and neuronal migration disorders (NMD) are well established in patients with medically intractable chronic partial epilepsy. We reviewed a series of 202 patients with temporal lobectomy to assess the incidence of dual pathology. To identify the abnormal neurons, cytomegalic or normal sized, immunohistochemical stains for neurofilament protein (NF-M/H) and microtubule associated protein 2 (MAP2), and Bielschowsky silver stains were routinely performed. The histopathological diagnosis of NMD was classified by the four grading system (J Neuropathol Exp Neurol 1998, 57 : 482). Strong immunoreactivity of NF-M/H was characteristically seen in the perikarya and mega or multiple dendrites of the abnormal neurons. Although MAP2 expressed in both normal and abnormal neurons and their dendrites, it was useful to identify loss of normal polarization of dendrites in the abnormal neurons. NF-M/H immunohistochemistry and silver stains were valuable to identify microscopic or occult lesions of NMD (grade II and III). MTS was identified in 158 cases (78.2%), and NMD in 127 cases

(62.9%). The pathological feature having both MTS and NMD was identified in 109 cases (54.0%). The frequency of NMD in MTS was about 70%. The feature of NMD was frequently found in MRI-invisible epileptogenic lesions. Results suggested that NMD might be a basic pathogenetic factor causing the temporal lobe epilepsy.

6. An experimental model of neuronal migration disorder by irradiation in rats

Neuronal migration disorders (NMDs) are the major underlying pathology of patients with medically intractable epilepsy. But, the role of NMDs on seizure susceptability or epileptogenecity has not been documented. We established an experimental model of NMDs in Wistar rats to demonstrate epileptogenic effect of the lesion, and further neurobiological studies of their pathogenesis. Foetal rats were exposed to 120 cGy external irradiation twice on day E16 and E18 of gestation. Histopathological examination revealed focal and/or diffuse cortical dysplasia consisting of dyslamination of the cerebral cortex and appearance of cytomegalic neurons, neuronal heterotopia in periventricular white matter, dispersion of the pyramidal layer and dentate gyrus of the hippocampus, and agenesis of corpus callosum. Abnormal expression of neurofilaments protein (NF-M/H) was characteristically observed in the dysplastic neurons of the neocortex and hippocampus. Seizure susceptability was tested by an intraeperitoneal injection of small dose of kainate (1 mg/kg). Prolonged ictal activity on EEG and clinical seizures were observed in the experimental animals. The histopathological change of the cerebral cortex and hippocampus correlated with the seizure activity. Reproducibility of the experiments was more than 90%. Results suggested that the experimental model would be useful to study the pathophysiology of NMDs.

중심 단어 : Disorder of cortical development (DCD), neuronal migration disorder (NMD) · Pathology · Grading · Experimental model.

■ **Acknowledgement**

I certainly appreciate the devotional efforts and cooperations of all members of the Honam Epilepsy Study Group considering the clinical and experinental data.

REFERENCES

1) Kuzniecky RI, Barkovich AJ. Pathogenesis and pathology of focal malformations of cortical development and epilepsy. *J Clin Neurophysiol* 1996;13:468-80.
2) Lee MC, Lee JS, Yang KH, Kim HI. Neuronal migvation disorder (NMD): Neuropathology and proposal for a grading system. *J Neuropathol Exp Neurol* 1998;57:482.
3) Lee MC, Lee JS, Kim HI, *et al.* Dual pathology of hippocampal sclerosis and neuronal migration disorder in patients with temporal lobe epilepsy. *Neuropathol Appl Neurobiol* 1999;25:69.
4) Lee MC, Lee JS, Choi HY, *et al.* An experimental model of neuronal migration disorder in the rat. *Neuropathol Appl Neurobiol* 1999;25:70.
5) Lee MY, Chung JH, Woo YJ, Kim HI, Lee MC. Cytoskeletal changes in cortical dysplasia. *Korean J Pathol* 2000;34:300-9.
6) Meencke HJ, Janz D. Neuropathological findings in primary generalized epilepsy: A study of eight cases. *Epilepsia* 1984;25:8-21.
7) Mischel PS, Nguyen LP, Vinters HV. Cerebral cortical dysplasia associated with pediatric epilepsy. Reiew of neuropathologic features and proposal for a grading system. *J Neuropathol Exp Neurol* 1995;54:137-53.
8) Sohn EJ, Kim SJ, Lee MC, Kim RI. Neuropathologic studies of cerebral cortical dysplasia. *J Korean Neurological Association* 1997;15:526-41.
9) Taylor DC, Falconer MA, Bruton CJ, Corsellis JAN. Focal dysplasia of the cerebral cortex in epilepsy. *J Neurol Neurosurg Psychiat* 1971;34:369-87.