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# Surgical outcome and prognostic factors of pediatric epilepsy caused by cortical dysplasia

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**Abstract** *Objects:* We analyzed 30 patients with cortical dysplasia (CD) and epilepsy to evaluate the clinical characteristics and surgical outcome of both epilepsy control and neurocognition. *Materials and methods:* The mean ages at seizure onset and at the time of the operation were 3.6 years (range, 1 month–12.6 years) and 10.3 years (range, 1.5–18.3 years), respectively. The mean follow-up period was 3.2 years (range, 1–5.3 years). $^{18}$FDG-positron emission tomography was the most sensitive and magnetic resonance imaging was the most specific in localizing the lesion. Developmental/intellectual delay was predominant in the early-onset group ($n$=18, seizure onset <3 years), with intelligence tending to be normal in the late-onset group ($n$=12, seizure onset ≥3 years). Mild CD predominated in the late-onset epilepsy group and moderate or severe CD in the early-onset group ($p$=0.005). The surgical success rate of epilepsy control was 87%. A better outcome was obtained if the lesion was confined to the temporal lobe. School performance was favorable in 43%. The age at seizure onset and preoperative developmental/intellectual delay were the important prognostic factors in school performance as well as the epilepsy control. A total of 77% of patients had relatively good social adaptation. Successful epilepsy control and good school performance were affirmative conditions precedent to social adaptation. *Conclusions:* Due to the favorable control of epilepsy and its effect on school performance and social adaptation, surgical treatment is strongly recommended for cortical dysplasia and intractable epilepsy.

**Keywords** Cortical dysplasia · Pediatric epilepsy · Surgical outcome · School performance · Social behavior · Prognostic factor

## Introduction

Cortical dysplasia (CD) designates a disorder in cortical development and organization with heterogeneous pathological findings, and its cause is not clearly understood [1, 16]. CD usually manifests initially with epilepsy, developmental delay, and focal neurological deficit in childhood. Although high-resolution magnetic resonance imaging (MRI) has recently allowed for the preoperative diagnosis of CD, the definitive diagnosis still depends on the histological findings after surgery for epilepsy [21]. The majority of recent studies on CD have focused on the pathogenesis and classification of the ultrastructural characteristics of the CD being well understood. The details of its clinical characteristics, however, have rarely been reported, especially in pediatric populations. Moreover, neither its prognostic value for

epilepsy control nor its neurocognitive outcome after surgery has been thoroughly discussed before, although they are clinically more important factors, especially in pediatric populations. In this study, we analyzed a series of pediatric patients with CD, histologically confirmed after surgery for epilepsy, to evaluate the clinical characteristics, prognostic factors, and surgical outcome for both epilepsy control and neurocognition. The preoperative value of imaging studies for CD was also investigated, especially focusing on the precise localization of the lesion.

## Materials and methods

The sample population for this study was obtained from a retrospective analysis of 30 pediatric patients (below 17 years of age) who had undergone epilepsy surgery between 1995 and 1999 at the Division of Pediatric Neurosurgery, Seoul National University Children's Hospital and were proven to have cortical dysplasia histologically. None of the patients responded to prolonged medical treatment so they were referred by the Department of Pediatrics for epilepsy surgery. Every operation was performed by the same surgeon (BKC). A histological diagnosis was made by the neuropathologist and was classified into three grades according to the severity using the grading system of Mischel et al. [16]. Preoperative evaluations, including MRI, interictal electroencephalogram (EEG), video-EEG monitoring, $^{18}$FDG-positron emission tomography (PET), inter-ictal and ictal $^{99m}$Tc-single photon emission computed tomography (SPECT) and neurocognitive function tests, were performed. To compare the sensitivity and localization capability of the neuroimaging studies, the results were classified into three groups relating to the histological results: (1) 'effective', when the study localized the lesion accurately with no false-positive areas when taking the cerebral lobe as the standard unit; (2) 'partially effective', when the positive area of the study included both the lesion and a false-positive area; and (3) 'not effective', when the study localized in an area other than the true lesion or the result was normal (a false negative). The number of effective and partially effective groups per number of patients having taken part in the study was defined as the sensitivity of the study. Follow-up data were gathered by telephone interviews of parents using standardized questions relating to the postoperative school performance and social adaptation (Table 1). Final establishment of surgical resection area was determined on the basis of invasive study unless the lesion was expected to be confined to the temporal lobe. Cortisectomy after the invasive study was performed in 18 patients, with a temporal lobectomy only being performed in 11 patients and a functional hemispherectomy in one patient. Repeated surgery was performed in three patients. The postoperative outcome of epilepsy control was assessed using the Engel classification [2]. Antiepileptic drug administration was continued regardless of postoperative outcome.

To evaluate the clinical outcome and prognostic factors, we categorized the population into four groups according to the age at seizure onset (early onset <3 years and late onset ≥3 years) and existence of developmental delay–intellectual delay (DD/ID): group 1, early onset and DD/ID (+); group 2, early onset and DD/ID(−); group 3, late onset and DD/ID(+); and group 4, late onset and DD/ID(−). We considered 3 years of age to be the criterion period of functional maturation of the normal brain. The patients were determined to have DD/ID based on the Wechsler Intelligence Scale for Children, as rated by a specialist, but this was substituted for an evaluation of developmental milestone, from a thorough neurological examination, if the patient was too young. A preoperative focal neurological deficit was only observed in two patients and was ignored in the statistical analysis. In addition, the relationships between clinical outcomes and various clinical variables, such as duration of epilepsy, lesion location, and histological grade of CD, were investigated. The chi-square method and Fisher's exact test were used for the statistical analyses.

**Table 1** Standardized questionnaire used in telephone interviews

| | |
|---|---|
| School performance | |
| How did the child make out the school records in the class? Choose one. | |
| 1. Good | Records ranked under 30% in ordinary class |
| 2. Average | Records ranked between 30 and 70% in ordinary class |
| 3. Bad | Records ranked more than 70% in ordinary class |
| 4. Specialized | Needed specialized class |
| Social adaptation | |
| How many intimate friends the child has? Choose one. | |
| 1. Good | More than 3 children, joined well with others |
| 2. Passive | 1 or 2 children, limited |
| 3. Bad | No friends, kept to him or herself |

## Results

### Patient demographics

Of 52 cases having undergone epilepsy surgery at the Division of Pediatric Neurosurgery, Seoul National University Children's Hospital at the same period, 30 (58%) were proven to have cortical dysplasia histologically. The male-to-female ratio was 1.72:1. The mean age at seizure onset was 3.6 years (range, 1 month–12.6 years), with 18 patients experiencing their first seizure before 3 years of age and 12 after then. The mean age at the time of the operation was 10.3 years (range, 1.5–18.3 years). The mean duration of illness, from the first seizure to the time of the operation, was 6.7 years (range, 1.4–17.6 years) and the mean follow-up period was 3.2 years (range, 1–5.3 years).

### Clinical characteristics

The patterns of epilepsy were characterized by a complex partial seizure in all patients, with 13 accompanied by generalized tonic–clonic propagation. A neurological examination revealed focal neurological deficit in only two patients. Seventeen patients had DD/ID in their preoperative examinations and the other 13 were normal in their neurocognitive evaluations. Thirteen of the 18 patients in the early-onset group showed DD/ID, while this was 4 of 12 in the late-onset group. This difference was on the borderline of being statistically significant ($p$=0.061, Table 2).

### Preoperative evaluation

Preoperative inter-ictal EEG revealed abnormal waves in all patients, with background slowing noted in 12 patients. Although epileptiform discharge in ictal EEG was found in all patients, only 12 (40%) were correctly localized to the epileptogenic lesion, whereas another 12 (40%) demonstrated seizure activity involving multiple lobes, including epileptogenic lesion, with the other six patients (20%) having false localization. The synthetic sensitivity of the EEG was 80%.

MRI, PET, and SPECT were performed in 30, 25, and 28 patients, respectively, and these techniques' overall sensitivities in localizing the epileptogenic lesions were 74 (22 of 30), 92 (23 of 25), and 64% (18 of 28), respectively, with the PET being the most sensitive ($p$=0.002). However, MRI (63%) surpassed PET (36%) in its preciseness of the above-mentioned localization for the 'effective group' (Table 3).

With the exception of the eight cases with normal findings, the MRI features were classified into focal (13 cases) and diffuse (nine cases) groups, according to whether the lesion was confined to a single lobe or not. The abnormal features of the MRI included: cortical thickening, mass lesion, subcortical lesion, cortical atrophy, gyral flattening, or a mixed composition of the above.

### Histological characteristics

Tumors were accompanied by CD in six patients (20%), and all were dysembryoplastic neuroepithelial tumors, with the exception of one ganglioglioma. The CD was histologically graded according to its severity: 14 cases (47%) were mild, 6 (20%) were moderate, and 10 (33%) were severe. Mild CDs predominated in the late-onset group, but there were more moderate or severe CDs in the early-onset group, which was statistically significant ($p$=0.005, Table 2). The lesion was limited in temporal lobe in 16 patients (53%). There were 13 patients (44%) who showed extratemporal lesion, including five patients (17%) of multilobar lesion, while hemispheric involvement was observed in one (3%). There was no significant difference in the distribution of histological grades of CD according to the lesion location ($p$=0.127). We were unable to verify any correlation between patterns of the MRI abnormalities (focal vs diffuse type) and the histological findings ($p$=0.298).

### Postoperative outcome: epilepsy control

Regarding the Engel classes I and II as a favorable outcome, the surgical success rate of epilepsy control was 87% (Table 4). The outcome was significantly more favorable in all patients whose lesion was limited to the temporal lobe, whereas other variables, such as histological grade, MRI findings, seizure onset-age, and DD/ID, were of no prognostic value (Table 5).

**Table 2** Distribution of developmental/intellectual delay (DD/ID) and histological grade according to seizure-onset age ($n$=30)

| Age of seizure onset | Developmental/intellectual delay (DD/ID) | | Histological grade of cortical dysplasia | | |
|---|---|---|---|---|---|
| | DD/ID(−) | DD/ID(+) | Mild | Moderate | Severe |
| Early onset (<3 years) | 5 | 13 | 4 | 5 | 9 |
| Late onset (>3 years) | 8 | 4 | 10 | 1 | 1 |
| $p$ value | | 0.061 | | | 0.005 |

**Table 3** Diagnostic value of preoperative localizing tools ($p$=0.002)

| | Effective | Partially effective | Not effective [nl] | Sensitivity | Number, $n$ |
|---|---|---|---|---|---|
| MRI | 19 (63%) | 3 (10%) | 8 [8] (27%) | 74% | 30 |
| PET | 9 (36%) | 14 (56%) | 2 [0] (8%) | 92% | 25 |
| SPECT | 10 (36%) | 8 (28%) | 10 [2] (36%) | 64% | 28 |

*nl* Normal

### Postoperative outcome: neurocognitive and social outcome

Table 4 shows the postoperative follow-up outcomes of school performance based on the results of the above-mentioned standardized questionnaires. The good and average groups were appraised as a superior class, with the rest as an inferior class. The best school performance was achieved in the late-onset group without DD/ID, followed successively by the early-onset group without DD/ID, the early-onset group with DD/ID, and the late-onset group with DD/ID ($p$=0.004, Table 6). There was borderline significance in the interrelation between epilepsy control rate and school performance ($p$=0.087, Table 6). However, there was no significant relation between the duration of illness, epilepsy control rate, or school performance. Postsurgical social adaptation was acceptable in 77% of patients, including the good and passive groups (Table 4). Social adaptation was also significantly correlated with epilepsy control rate and school performance (Table 7). The favorable prognostic factors and their relationships are summarized in Fig. 1. Postoperative KPS was above 90 in 73% of patients.

### Postoperative outcome: operative complications

Five patients suffered from wound or cerebrospinal fluid infections, two experienced temporary hemiparesis or facial paresis, and there was a subdural hygroma in one. However, no serious complications were encountered. The long-term follow-up of serial intellectual quotient tests revealed a worsening score over time in two patients, but we were unable to verify the exact cause.

## Discussion

Although the exact prevalence of CD is unknown, it has been reported to be found diversely in 1.8 to 34% of patients having undergone surgery for epilepsy and is more frequent in children [10, 15, 19]. Leventer et al. [14] reported no differences in the prevalence between male and female children, compared to its female predominance in adults. The relatively high frequency of CD (58% of epilepsy surgery) and its male predominance in our series need to be verified by more comprehensive studies. The reported rate of combined tumor and CD was 4 to 7.5% in all cases of epilepsy surgery, which was somewhat lower than 20% in our series [3, 17]. Leventer et al. [14] presented the frontal lobe as the most frequently affected area due to the fact that it occupies the largest area of brain tissue. Hirabayashi et al. [7] reported that CD frequently

**Table 4** Postsurgical outcome in cortical dysplasia ($n$=30)

| Grade | Number of cases | Outcome |
|---|---|---|
| Epilepsy control | | |
| Engel class I | 20 (67%) | Favorable 87% |
| Engel class II | 6 (20%) | |
| Engel class III | 1 (3%) | Unfavorable 13% |
| Engel class IV | 3 (10%) | |
| School performance | | |
| Good | 3 (10%) | Superior 43% |
| Average | 10 (33%) | |
| Bad | 9 (30%) | Inferior 57% |
| Specialized | 8 (27%) | |
| Social adaptation | | |
| Good | 14 (47%) | Acceptable 77% |
| Passive | 9 (30%) | |
| Bad | 7 (23%) | Unacceptable 23% |

**Table 5** Postsurgical epilepsy control outcome with relation to multiple variables ($n$=30)

| Variables | Epilepsy control outcome | | $p$ value |
|---|---|---|---|
| | Favorable | Unfavorable | |
| Area | | | |
| Temporal | 16 | 0 | 0.037 |
| Extra-temporal | 10 | 4 | |
| Seizure-onset age and developmental/intellectual delay | | | |
| Early onset, DD/ID(+) | 12 | 1 | 0.167 |
| Early onset, DD/ID(−) | 5 | 0 | |
| Late onset, DD/ID(+) | 2 | 2 | |
| Late onset, DD/ID(−) | 7 | 1 | |
| Histological grade | | | |
| Mild | 11 | 3 | 0.513 |
| Moderate | 6 | 0 | |
| Severe | 9 | 1 | |
| MRI findings | | | |
| Focal | 13 | 0 | 0.169 |
| Diffuse | 7 | 2 | |
| Normal | 6 | 2 | |

affected extratemporal areas. However, we found the temporal lobe to be the most frequently affected area, which corresponds with the studies of Keene et al. [10].

Of all the non-invasive methods, MRI has been shown to be the most effective imaging tool in the diagnosis of CD, with a reported sensitivity of between 50 and 70% [21]. Cortical thickening with or without signal change, abnormal gyral formation, and focal subcortical signal changes have been reported as common MRI findings of focal CD [13, 23]. Tassi et al. [18] suggested that highly epileptogenic zones may not have been revealed by neuroimaging in their clinical analysis of CD. As mentioned above, PET (92%) was more sensitive than MRI (74%) in diagnosing CD when both the effective and partially effective groups were regarded as being successful. PET dominates for the rough screening and localization of lesions. However, when considering the effective group only, MRI surpassed

**Table 6** Postsurgical school performance in relation to seizure-onset age, developmental/intellectual delay(DD/ID), and epilepsy control outcome ($n$=30)

| | School performance | | $p$ value |
|---|---|---|---|
| | Superior | Inferior | |
| Seizure-onset age and developmental/intellectual delay (DD/ID) | | | |
| Early onset, DD/ID(+) | 3 | 10 | 0.004 |
| Early onset, DD/ID(−) | 3 | 2 | |
| Late onset, DD/ID(+) | 0 | 4 | |
| Late onset, DD/ID(−) | 7 | 1 | |
| Epilepsy control outcome | | | |
| Favorable (Engel class I and II) | 13 | 13 | 0.087 |
| Unfavorable (Engel class III and IV) | 0 | 4 | |

**Table 7** Relationship between postsurgical social adaptation and school performance, epilepsy control, seizure-onset age, and developmental/intellectual delay (DD/ID) ($n$=30)

| | Social adaptation | | $p$ value |
|---|---|---|---|
| | Acceptable | Unacceptable | |
| Seizure-onset age and developmental/intellectual delay | | | |
| Early onset, DD/ID(+) | 9 | 4 | 0.145 |
| Early onset, DD/ID(−) | 4 | 1 | |
| Late onset, DD/ID(+) | 2 | 2 | |
| Late onset, DD/ID(−) | 8 | 0 | |
| Epilepsy control | | | |
| Favorable | 22 | 4 | 0.051 |
| Unfavorable | 1 | 3 | |
| School performance | | | |
| Superior | 13 | 0 | 0.010 |
| Inferior | 10 | 7 | |

PET. This means MRI is superior to PET for the accurate localization of lesion, which can be helpful in the actual planning of an operation, but rather high false-negative rates are a problem. Therefore, we can expect a synergistic effect in the diagnoses and localization of a lesion if MRI and PET are used simultaneously. Kim et al. [11] concluded that PET is more useful in delineating the cortical abnormality in patients with mild degrees of focal CD. Lee et al. [13] also put a high value upon PET for its supplementary and confirmatory diagnostic roles in the localization of epileptogenic foci in CD, especially when the results from MRI are normal.

It is generally understood that the surgical outcome for epilepsy is worse if CD is found in the epileptic zone [16]. However, the favorable control of epilepsy (Engel classes I and II) with CD was shown to be as high as 87% in our series. This result suggests that the location and the extent of the lesion are reasonably important prognostic factors

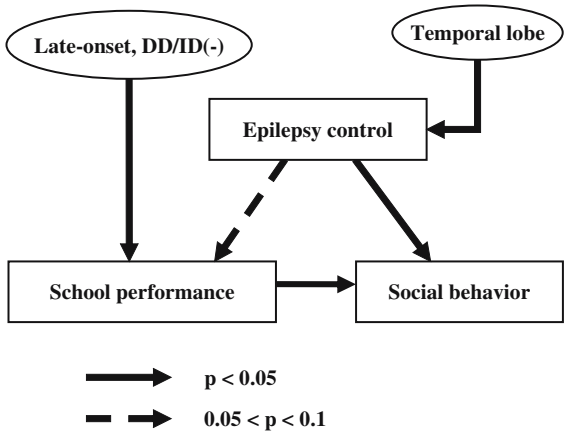


**Fig. 1** Summary of the significant favorable prognostic factors of surgical outcome and their reciprocal relationships

compared with CD alone. Despite our results, some studies have demonstrated that the postoperative outcome of epilepsy control is related to the histological grade of CD [5, 9]. Keene et al. [10] reported that the histological grade was irrelevant to the surgical outcome. In our current work, there was no significant difference in the postoperative outcome of epilepsy control between the early- and late-onset groups, although moderate and severe grades of CD predominated in the early-onset group. This also supports the deduction that the histological grade of CD, which is related to seizure onset age, has no influence on the surgical outcome of epilepsy control. The superior epilepsy control with a temporal lobe location of the CD, compared to an extra-temporal location, corresponds with other reports on general epilepsy surgery. However, we were unable to analyze the effect of multilobar or extra-temporal lesions in relation to the surgical outcome due to the limited amount of relevant data.

School performance was significantly influenced by both the age at seizure onset and the existence of DD/ID at operation so these are important prognostic factors for determining the quality of life. Bartolomei et al. [1] cited that CD patients with a late onset of seizure (above the age of 12) showed less DD/ID but a better social life than patients with an early onset, with the age at the seizure onset being an important prognostic factor. The early onset of seizure has been reported as an unfavorable prognostic factor for the cognitive outcome [4, 12, 22]. These results are exactly in accordance with our work, although the age criterion was somewhat different. It seems that neurological injury from epilepsy before the age of 3 years, which is the critical period for the higher function of neurological development, is the major cause of poor neurocognitive function. However, three patients in the early-onset group with DD/ID in our study improved their school performance and held high ranks in their classes after their operations. It is also worth noting that they all had lesion confined to the right temporal lobe and underwent a right temporal lobectomy. Westerveld et al. [20] reported improvement in nonverbal intellectual functioning after a temporal lobectomy, and Ivnik et al. [8] also found improvement in neurocognitive function especially after a right temporal lobectomy. Therefore, a more favorable neurocognitive outcome is expected in a patient with a lesion confined to the temporal lobe, and surgery must be actively considered in such patients, even if DD/ID already exists.

The time of surgery was thought to be an insignificant prognostic factor due to the discrepancies between the duration of epilepsy morbidity and the neurocognitive outcome. Hennessy et al. [6] also mentioned that cognitive and behavioral dysfunctions are associated with lower epilepsy control rates, which were independent of the duration of epilepsy, for the surgical outcomes of temporal lobe epilepsy in a large study population. However, it is recommended that surgery should be actively considered before school age if medical treatment has failed because complete epilepsy control is important not only for school performance but also for social adaptation.

## Conclusion

Pediatric epilepsy, caused by CD, is well controlled by surgical treatment, which is recommended for medically intractable epilepsy due to the control of epilepsy being important in school performance and social adaptation. Mild CD predominated in the late-onset group, with more moderate or severe CD in the early-onset group. MRI and PET are complementary to each other for the preoperative localization of the epileptogenic foci. The temporal lobe location was a favorable prognostic factor for epilepsy control. The age at seizure onset and the existence of DD/ID before an operation were important prognostic factors for a cognitive outcome.

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