**Original** article

Folia Neuropathologica

# Malformations of cortical development in children: clinical manifestation, neuroimaging and neuropathology in selected cases

**Ewa Emich-Widera[1], Dawid Larysz[2], Ewa Kluczewska[3], Patrycja Larysz[2], Dariusz Adamek[4], Marek Mandera[2], Elżbieta Marszał[1]**

[1]Department of Paediatrics and Developmental Neurology, Silesian Medical University, Katowice, Poland; [2]Department of Paediatric Neurosurgery, Silesian Medical University, Katowice, Poland; [3]Department of Radiological Imaging, Silesian Medical University, Katowice, Poland; [4]Department of Neuropathology, Institute of Neurology, Jagiellonian University, Medical College, Cracow, Poland

*Folia Neuropathol 2006; 44 (4): 307–313*

## Abstract

*Cerebral cortical development can be divided into three steps: cellular proliferation, neuronal migration and organization. Based on known pathologic, genetic and neuroimaging features a classification for malformations of cortical development was proposed by Barkovich in 2001, and updated in 2005. Malformations of cerebral cortex development (MCCD) often demonstrate epileptic seizures and delay in psychomotor development. About 20–40% of children with epilepsy are drug-resistant and there is a large paediatric population requiring epilepsy surgery operations. In our work we performed clinical analysis of 68 children with MCCD treated in our hospital between 2000 and 2006. In our work to consider the type of MCCD we used the updated classification scheme proposed by Barkovich et al. We analyzed epilepsy, gestational and perinatal history, initial symptoms, time to establishing full diagnosis and neurodevelopmental/IQ status. In our results we found that despite similar clinical manifestation neuropathological basis could be significantly different, and vice versa: children with nearly identical neuropathological findings could have completely different neurological and radiological symptoms. Children with drug-resistant epilepsy are potential candidates for neurosurgical treatment; especially lesionectomies in such cases could be very promising in terms of epilepsy management and quality of life as well.*

***Key words:*** *focal cortical dysplasia, epilepsy, children*

## Introduction

Cerebral cortical development is a complex process, which can be divided into three broad and overlapping embryological steps: cellular proliferation in the germinal zones, neuronal migration of cells to the developing cerebral cortex and vertical and horizontal organization of cells within the cortex with the establishment of axonal and dendritic ramifications. Based on these fundamental stages of cortical formation, a classification for malformations of cortical mantel was proposed [4,5]. The classification was made based on known pathologic, genetic and neuroimaging features, giving a framework for known and unknown malformations, which could be added to

**Communicating author:**
Dawid Larysz, MD, Dept. of Paediatric Neurosurgery, Silesian Medical University, ul. Medyków 16, 40-752 Katowice, Poland, tel. +48 501 336 296, e-mail: dawilar@poczta.onet.pl

the subscales of the classification as knowledge advanced. The classification is weighted toward imaging data as it is available for all diagnosed patients. The neuroimaging component allows the scheme to be applied also to patients without brain biopsy as in classification based on histopathological examinations. It is worth emphasizing that the three major steps of cortical development are not temporally separated. The proliferation continues after the beginning of migration and migration continues as organization begins. It is impossible to differentiate abnormal brain size secondary to changes in proliferation from that secondary to abnormal apoptosis or a combination of both. A significant change, since the prior classification, is the elimination of the subdivision of the three major categories into (A) diffuse malformations and (B) focal/multifocal malformations. Diffuse and localized brain malformation may result from the same underlying processes with differences in phenotype.

Malformations of cerebral cortex development (MCCD) are often associated with severe epilepsy, with onset during childhood, and developmental delay [1,7,12]. However, prevalence and severity of epilepsy is variable in different malformations [11]. About 20–40% of children with drug-resistant epilepsy harbour a cortical malformation, and up to 50% of paediatric epilepsy surgery operations are carried out in children with an MCCD [10,12]. Moreover, children with MCCD are one of the largest paediatric populations in which epilepsy surgery operations are needed. Satisfactory effects are seen in cases of focal cortical dysplasia (FCD), where in up to 90% of patients the lesionectomy is followed by remission [9,10].

In this paper we perform a clinical analysis of 68 children diagnosed with MCCD treated in our hospital, considering type of MCCD, presence of epilepsy and its characteristics, gestational and perinatal history, initial symptoms and time to establishing full diagnosis. We also analyze neurodevelopmental/IQ status. For better illustration of the clinical problem we present two children with drug-resistant epilepsy caused by MCCD, treated with neurosurgical lesionectomy. For these cases accurate histopathological examinations and neuroradiological studies are presented.

## Material and methods

Between 2000 and 2006 in the Department of Developmental Neurology and Department of Paediatric Neurosrugery of Silesian Medical University in Katowice 68 children were treated because of malformation of cortical development. In our work we used the updated classification scheme proposed by Barkovich et al. [4,5]. In this classification malformations of cortical development are based also on the step at which the development was disturbed. It consists of four major groups: I – malformations due to abnormal neuronal and glial proliferation or apoptosis, II – malformations due to abnormal neuronal migration, III – malformations due to abnormal cortical organization (including late neuronal migration), IV – malformations of cortical development not otherwise classified. The following malformations based on the updated Classification Scheme [4,5] were recognized:

- IC1(?) – abnormal proliferation – non-neoplastic – without histopathological confirmation
- IC1a – abnormal proliferation – non-neoplastic – cortical hamartomas of tuberous sclerosis
- IIC1 – abnormal cell migration – subependymal (periventricular) heterotopia
- IIC2 – abnormal cell migration – subcortical heterotopia
- IIA – lissencephaly/subcortical band heterotopia spectrum
- IIIA1 – abnormal cortical organization – bilateral polymicrogyria syndrome
- IIIA2 – abnormal cortical organization – shizencephaly
- IIIA3 – abnormal cortical organization – polymicrogyria with other brain malformations
- IIIA4 – abnormal cortical organization – polymicrogyria as part of multiple congenital anomaly
- IVB2 – malformations of cortical development not otherwise classified

Full characteristics of the studied group are presented in Table I.

## Results

The most frequent reasons for admission to hospital were epilepsy, which appears in 37 children, and neurodevelopmental delay in 24 cases. Nearly half of studied patients have abnormal gestational or perinatal history (Table II).

Drug resistance of epilepsy was found mainly in IC1a type. In this group of patients infantile spasms were observed in 85% of children. The largest groups of children were: those with type II malformation –

**Table I.** Characteristics of study group

| Type of malformation | Number of cases | Age of seizure onset (months) | Age of MCCD diagnosis (months) | IQ (median) | Gender | |
|---|---|---|---|---|---|---|
| | | | | | F | M |
| IC1(?) | 2 | 18 (18–18) | 39 (18–60) | 90 (80–100) | 1 | 1 |
| IC1a | 9 | 19 (19–19) | 22 (6–50) | 63 (10–105) | 6 | 3 |
| IIC1 | 6 | 10 (1–36) | 18 (1–36) | 61 (36–98) | 3 | 3 |
| IIC2 | 5 | 60 (4–166) | 82 (20–172) | 48 (12–100) | 1 | 4 |
| IIA | 13 | 10 (1–36) | 50 (6–192) | 55 (10–103) | 6 | 7 |
| IIIA1 | 1 | – | 78 (78–78) | 47 (47–47) | 1 | 0 |
| IIIA2 | 10 | 35 (1–124) | 72 (1–165) | 69 (16–90) | 6 | 4 |
| IIIA3 | 11 | 25 (1–132) | 65 (4–144) | 57 (11–109) | 1 | 10 |
| IIIA4 | 2 | 1 (1–1) | 70 (9–131) | 34 (18–50) | 0 | 2 |
| IVB2 | 9 | 13 (1–84) | 84 (1–146) | 65 (29–98) | 5 | 4 |

**Table II.** Division of group depending on gestational history and major reason for hospitalization/provisional diagnosis

| Type of malformation | Gestational/Perinatal history | | Reason for hospitalization/Provisional diagnosis | | |
|---|---|---|---|---|---|
| | abnormal | normal | epilepsy | neurodev. delay | other |
| IC1(?) | 1 | 1 | 2 | 0 | 0 |
| IC1a | 3 | 6 | 6 | 2 | discolouration of the skin (1) |
| IIC1 | 4 | 2 | 3 | 3 | 0 |
| IIC2 | 3 | 2 | 3 | 0 | problems in school (1) |
| IIA | 7 | 5 | 7 | 5 | hemiparesis, dysmorphy (1) |
| IIIA1 | 1 | 0 | 0 | 1 | 0 |
| IIIA2 | 2 | 4 | 8 | 1 | hemiparesis |
| IIIA3 | 4 | 7 | 7 | 3 | convergent squint (1) |
| IIIA4 | 1 | 1 | 0 | 2 | 0 |
| IVB2 | 5 | 4 | 1 | 7 | behavioural disorders and headaches(1) |

malformations due to abnormal neuronal migration – 24 patients; and type III – abnormal cortical organization – 22 patients.

Analysis of IQ examinations revealed that the group of children with polymicrogyria as part of multiple congenital anomaly had the worse outcome, with median 34. Also with poor IQ outcome were children with bilateral polymicrogyria syndrome (median 47) and with subcortical heterotopia (median 48). The highest IQ was observed in children with IC1(?); the median was 90. The detailed data are shown in Table I. Data

**Table III.** Characteristics of epilepsy depending on type of cortical malformation

| Type of malformation | Epilepsy | | Type of seizure (% in specific type of malformation) | | | Refractory epilepsy | |
|---|---|---|---|---|---|---|---|
| | yes | no | generalized | partial spasms | infantile | yes [%] | no [%] |
| IC1(?) | 2 | 0 | 0 | 100 | 0 | 50 | 50 |
| IC1a | 7 | 2 | 0 | 14.3 | 85.7 | 71.4 | 28.6 |
| IIC1 | 3 | 3 | 0 | 75 | 25 | 0 | 100 |
| IIC2 | 3 | 2 | 0 | 100 | 0 | 0 | 100 |
| IIA | 10 | 3 | 37.5 | 0 | 62.5 | 33.3 | 66.7 |
| IIIA1 | 1 | 0 | 100 | 0 | 0 | 0 | 100 |
| IIIA2 | 9 | 1 | 66.7 | 33.3 | 0 | 22.2 | 77.8 |
| IIIA3 | 9 | 2 | 71.4 | 14.3 | 14.3 | 42.9 | 57.1 |
| IIIA4 | 1 | 1 | 0 | 0 | 100 | 0 | 100 |
| IVB2 | 5 | 4 | 20 | 80 | 0 | 20 | 80 |

considering presence of epilepsy, type of seizures and their drug-resistance are presented in Table III. Four children suffered from drug-resistant epilepsy caused by focal cortical dysplasia. All of those children underwent epilepsy surgery – lesionectomy. In a short time after surgery we observed decreased frequency of seizures and changes in seizure morphology to less intense and shorter. The good treatment results concerned not only neurological status but also improvement of quality of life.

In statistical analysis we did not find any significant correlations between type of MCCD and specific clinical manifestation. In our group of children we did not reveal significant correlation between type of seizure and type of MCCD. Moreover it seems that also type of MCCD does not determine type of epilepsy or its drug resistance.

To illustrate the clinical problem of MCCD we present two children who suffered from refractory epilepsy of MCCD origin successfully treated with neurosurgical procedures.

## Case 1.

B.G. 10-year-old boy.

The first epileptic fit (complex partial) occurred at the age of 6 years. MRI examination revealed a small proliferative lesion in the cortical layer of the right temporal lobe which was hyperintense in SE/T2 sequence (Fig. 1A) and hypointense in SE/T1 sequence (Fig. 1B). In the sagittal plane we can see malformation of the gyri formation (Fig. 1C). The lesion was hyperintense after contrast enhancement (Fig. 1D). EEG and SPECT findings confirmed the origin of epilepsy in the right temporal lobe. Despite many changes of AEDs seizures remained stable. His IQ was slightly below normal range. The boy was operated on. We performed a temporal craniotomy and lesionectomy. Histopathological examination revealed abnormal cortical layer pattern. In the histopathological specimen balloon cells characteristic for focal cortical dysplasia were present (Fig. 2). The postoperative follow-up was without complications. Control MRI examination revealed presence of a small amount of residual tumour. The boy was reoperated on in order to remove the lesion totally. At present (two years after the reparation) he takes only Tegretol and remains without seizures.

## Case 2.

K.M. 7-year-old-girl

From 8 months of life she presented epileptic fits, at first simple partial right-sided and then with complex partial seizures added. The child was treated pharmacologically. Many times AED were changed. Despite polypharmacotherapy the outcome was poor. Before hospitalization there were a dozen seizures per

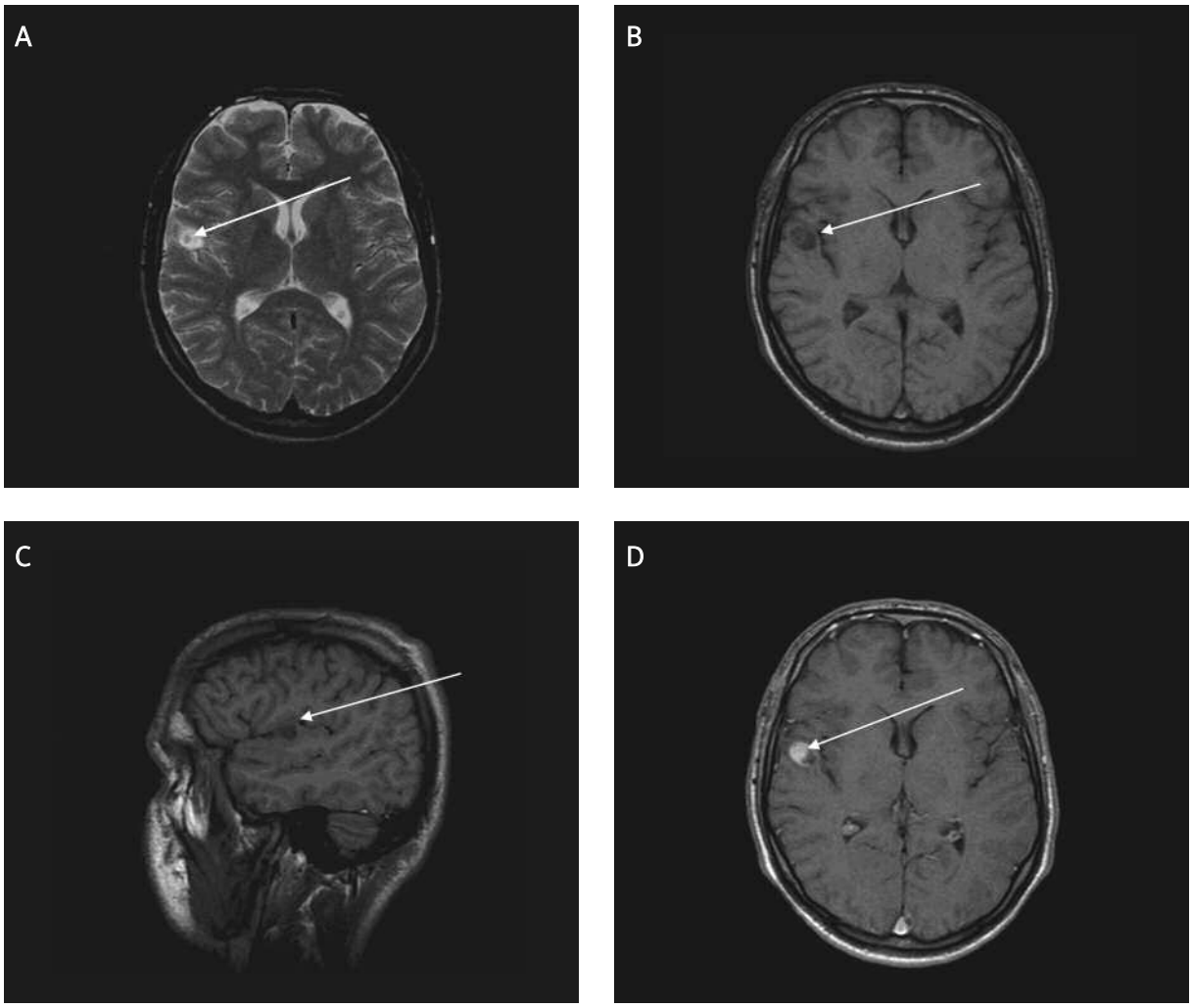


**Fig. 1.** MRI examination of the 10-year-old boy with intractable epilepsy; **A)** SE/T2 sequence, **B)** SE/T1 sequence, **C)** Sagittal SE/T1 scan, **D)** Contrast enhancement of the lesion

twenty-four hours. MRI examination revealed a lesion in the base of the left frontal lobe. In SE/PD (Fig. 3A) and SE/T2 (Fig. 3B) sequences there were noticeable abnormal formed cortical gyri in the base of left frontal lobe. In SE/T1 sequence abnormal architecture of the frontal lobe is visible (Fig. 3C). SPECT examination revealed depletion of radioisotope uptake in basal parts of the left frontal and temporal lobes. In EEG pathological bioelectricity of brain cortex was confirmed especially in the left fronto-temporal region. Neuropsychological evaluation revealed developmental delay. The girl was operated on with diagnosis of intractable epilepsy at the age of 4. Left frontal lesionectomy was performed. In histopathological examination we found signs of focal cortical dysplasia (Fig. 4). Neuronal atypia with large dysplastic neurons

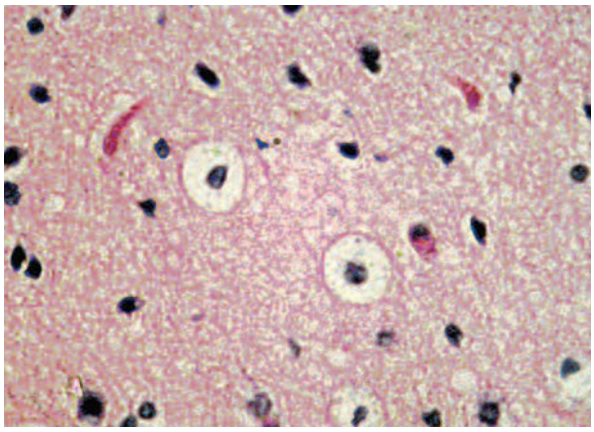

**Fig. 2.** Histopathological findings – abnormal cortical layer pattern with characteristic balloon cells. HE. Magn.x 400

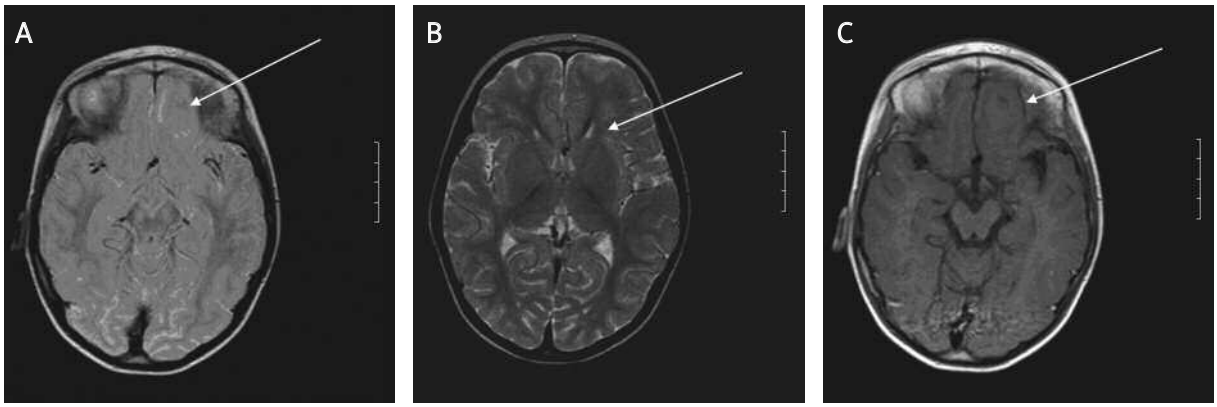


**Fig. 3.** MRI examination of the girl with intractable epilepsy. **A)** lesion in base of the left frontal lobe in SE/PD sequence, **B)** lesion in base of the left frontal lobe in SE/T2 sequence, **C)** lesion in base of the left frontal lobe in SE/T1 sequence

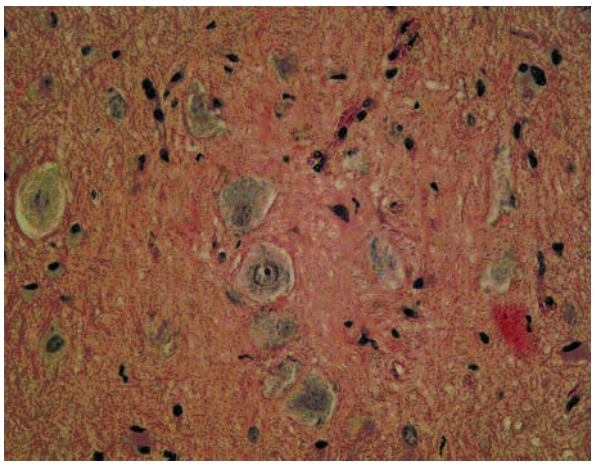

**Fig. 4.** Histopathological examination – neuronal atypia with large dysplastic neurons and polymorphic astrocytes. HE. Magn.x 400

were present. Also present in the specimen were polymorphic astrocytes. The postoperative follow-up was without complications. In a short time after surgery seizures significantly diminished in frequency and improved their morphology. Control MRI revealed proper postoperative status. At present the girl suffers only one absence fit a day. There was significant improvement in neurodevelopmental status.

## Discussion

Focal cortical dysplasia (FCD) is a peculiar developmental anomaly of the cortex, first identified by Taylor in refractory epilepsy patients after lobectomy [13]. Since those days several different systems (sometimes confusing) have been used for proper classification of malformations of cerebral cortex development. The cortical malformations previously grouped under the general term of neuronal migration disorders are currently diversified to reflect the improved knowledge of the pathological substrate, the possible aetiological factors and the relationship between altered structural features of the malformation and type of epilepsy. Nevertheless, despite many efforts it is still widely recognized that the classification of these disorders is far from satisfactory and there is no general consensus on these complex structural abnormalities. Furthermore, their aetiology is often uncertain and the mechanisms by which they generate epilepsy are unclear [3,10]. Avoli et al. revealed that brain samples obtained during surgery from focal cortical dysplastic tissue have an intrinsic ability to generate ictal-like epileptiform events when challenged with the convulsant drug 4-aminopyridine [3]. On the other hand Andres et al. proposed that severe cortical dysplasia associated with epilepsy could be the consequence of excess neurogenesis and postnatal retention of some preplate neurons, and this process probably occurs in late corticoneurogenesis [2]. Moreover, despite the knowledge about classical histopathological findings such as laminar cortical disruption, undifferentiated cells, giant and/or dysmorphic neurons, and balloon cells [12], outcome and natural history of the disease are frequently very difficult to predict. Similarly, neuroradiological findings, such as gyration anomalies, focal thickenings of the cortex, abnormal signal intensity in the cortex and in subcortical white matter in MRI, do not give us proper and full information about the clinical course of the disease [6,8]. In our

study group we did not reveal any significant relationships between type of MCCD and type of seizure morphology or clinical outcome. Four children diagnosed with MCCD were operated on for intractable epilepsy. All of them had focal cortical dysplasia confirmed both in neuroradiological findings as well as in histopathological examination. In all four cases postoperative clinical outcome was promising. The children have significantly fewer seizures and with better morphology. Moreover, we also observed an improvement in health-related quality of life [11]. Similar findings are confirmed in the literature [10]. It seems that further prospective multicentre studies including neuroradiological, histopathological, electrophysiological and neurological examinations are needed to better understanding this severe problem.

## Conclusions

1. The most frequent manifestations of malformation of cortical and white matter development are epilepsy and neurodevelopmental delay.
2. Despite similar clinical manifestation neuropathological basis could be significantly different, and vice versa: many children with nearly identical neuropathological findings could have completely different neurological and radiological symptoms.
3. Children diagnosed with malformation of cortical and white matter development who suffer from drug-resistant epilepsy are potential candidates for neurosurgical treatment. Clinical results of lesionectomies in such cases could be very promising in terms of epilepsy management and quality of life as well.

### References


1. Adamek D, Korzeniowska A, Morga R, Lopatka P, Jelenska-Szygula I, Danilewicz B. Dysembryoplastic neuroepithelial tumour (DNT). Is the mechanism of seizures related to glutamate? An immunohistochemical study. Folia Neuropathol 2001; 39: 111–117.
2. Andres M, Andre VM, Nguyen S, Salamon N, Cepeda C, Levine MS, Leite JP, Neder L, Vinters HV, Mathern GW. Human cortical dysplasia and epilepsy: an ontogenetic hypothesis based on volumetric MRI and NeuN neuronal density and size measurements. Cereb Cortex 2005; 15: 194–210.
3. Avoli M, Louvel J, Mattia D, Olivier A, Esposito V, Pumain R, D'Antuono M. Epileptiform synchronization in the human dysplastic cortex. Epileptic Disord 2003; 5 Suppl 2: S45–S50.
4. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. A developmental and genetic classification for malformations of cortical development. Neurology 2005; 27; 65: 1873–1887.
5. Barkovich AJ, Kuzniecky RI, Jackson GD, Guerrini R, Dobyns WB. Classification system for malformations of cortical development: update 2001. Neurology 2001; 57: 2168–2178.
6. Cepeda C, Andre VM, Flores-Hernandez J, Nguyen OK, Wu N, Klapstein GJ, Nguyen S, Koh S, Vinters HV, Levine MS, Mathern GW. Pediatric cortical dysplasia: correlations between neuroimaging, electrophysiology and location of cytomegalic neurons and balloon cells and glutamate/GABA synaptic circuits. Dev Neurosci 2005; 27: 59–76.
7. Dambska M, Rafalowska J. Neuronal heterotopies and formation of cortical anomalies. Folia Neuropathol 2003; 41: 217–221.
8. Francione S, Vigliano P, Tassi L, Cardinale F, Mai R, Lo Russo G, Munari C. Surgery for drug resistant partial epilepsy in children with focal cortical dysplasia: anatomical-clinical correlations and neurophysiological data in 10 patients. J Neurol Neurosurg Psychiatry 2003; 74: 1493–1501.
9. Guerrini R, Holthausen H, Parmeggiani L, Chiron C. Epilepsy and malformations of the cerebral cortex. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (eds.). Epileptic Syndromes in Infancy, Childhood and Adolescence. 3rd ed. John Libbey, London 2002; pp. 457–479.
10. Kral T, Clusmann H, Blumcke I, Fimmers R, Ostertun B, Kurthen M, Schramm J. Outcome of epilepsy surgery in focal cortical dysplasia. J Neurol Neurosurg Psychiatry 2003; 74: 183–188.
11. Larysz D, Larysz P, Mandera M. Evaluation of quality of life and clinical status of children operated on for intractable epilepsy. Childs Nerv Syst 2006; [Epub ahead of print].
12. Tassi L, Colombo N, Garbelli R, Francione S, Lo Russo G, Mai R, Cardinale F, Cossu M, Ferrario A, Galli C, Bramerio M, Citterio A, Spreafico R. Focal cortical dysplasia: neuropathological subtypes, EEG, neuroimaging and surgical outcome. Brain 2002; 125: 1719–1732.
13. Taylor DC, Falconer MA, Bruton CJ, Corsellis JA. Focal dysplasia of the cerebral cortex in epilepsy. J Neurol Neurosurg Psychiatry 1971; 34: 369–387.