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Polymicrogyria: A Clinical and Experimental Approach to Epilepsy

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1. Introduction

Polymicrogyria is the presence of an excess number of abnormally small gyri that produce an irregular cortical surface. Although polymicrogyria is associated with severe epilepsy in 65% of patients (Guerrini & Filippi, 2005), few data concerning the epileptogenic zone and its relationship with the polymicrogyric tissue are available due to the fact that patients with polymicrogyria are rarely considered to be suitable candidates for epilepsy surgery (Chassoux et al., 2008). An experimental model in which a single or few microgyri are generated by a freezing insult suggests a widespread area of functional disruption that extends beyond the visualized abnormality (Redecker et al., 2000). However, the detailed mechanism of epileptogenesis has not yet been well characterized for polymicrogyria (Sisodiya, 2004). In this chapter, clinical and experimental investigations in polymicrogyria were reviewed with special reference to the epileptogenicity of this malformation.

2. Definition and pathogenesis of polymicrogyria

Polymicrogyria is a cerebral cortical malformation characterized by an excessively folded cortical ribbon of miniature, individually thin convolutions, which may be fused together or piled on top of one another (Sisodiya, 2004). The cortical surface is irregular, and the convolutions can appear wider than expected, with a bumpy surface, like cobblestones or morocco leather (Graham & Lantos, 2002). There are two subtypes: unlayered type and four-layered type. In unlayered polymicrogyria, the external molecular layer is continuous and does not follow the profile of the convolutions, and the underlying neurons have radial or vertical distribution but no laminar organization (Ferrer, 1984). Polymicrogyric area may be distributed by focal, multi-lobar, or diffuse in the cerebral cortex. This brain malformation is thought either to be resulted from early exogenous insult from the 13th to 18th week of gestation or to be genetically determined (Ferrer & Catala, 1991). In four-layered polymicrogyria, there are two neuronal layers (2nd and 4th layers) under the molecular layer (1st layer), separated by an intermediate layer with many fibers and few cells (cell-sparse 3rd layer) (Graham & Lantos, 2002). Polymicrogyric 2nd and 3rd layers are thought to be correspond to the normal cortical layers II, III, IV, and layer V, respectively, in which horizontal neuronal lamination is usually spared. Four-layered polymicrogyria is believed to be resulted from a perfusion failure limited to one or more arterial vascular beds, occurring between the 20th and 24th week of gestation. This would lead to intracortical

laminar necrosis with delayed damage of the distal section of radial glial fibers, with consequent late migration disorder and post-migratory overturning of cortical organization (French, 1989).

Experimental polymicrogyria can be modeled by the excitotoxic brain lesions during the period of neuronal migration. Ibotenate is an agonist of the N-methyl-D-aspartate (NMDA) complex receptor. Experimental studies have demonstrated that an intracerebral injection of ibotenate induces excitotoxic brain lesions mimicking a variety of neuronal migration disorders including microgyria (Takano et al., 2005). After the radial glial fibers and surrounding neural tissues were damaged by ibotenate, the corresponding area within the cortical plate collapsed (Figure 1A). As the surrounding neurons migrate along the radial fibers, the cortical plate rolled inward and became infolded, forming microgyria (Figure 1B). Thus, the damage to intermediate cortical layers would produce a difference in growth rate between outer and inner cortical layers, with consequent excessive folding of the cortical surface (Figure 1C) (Takano et al., 2005).

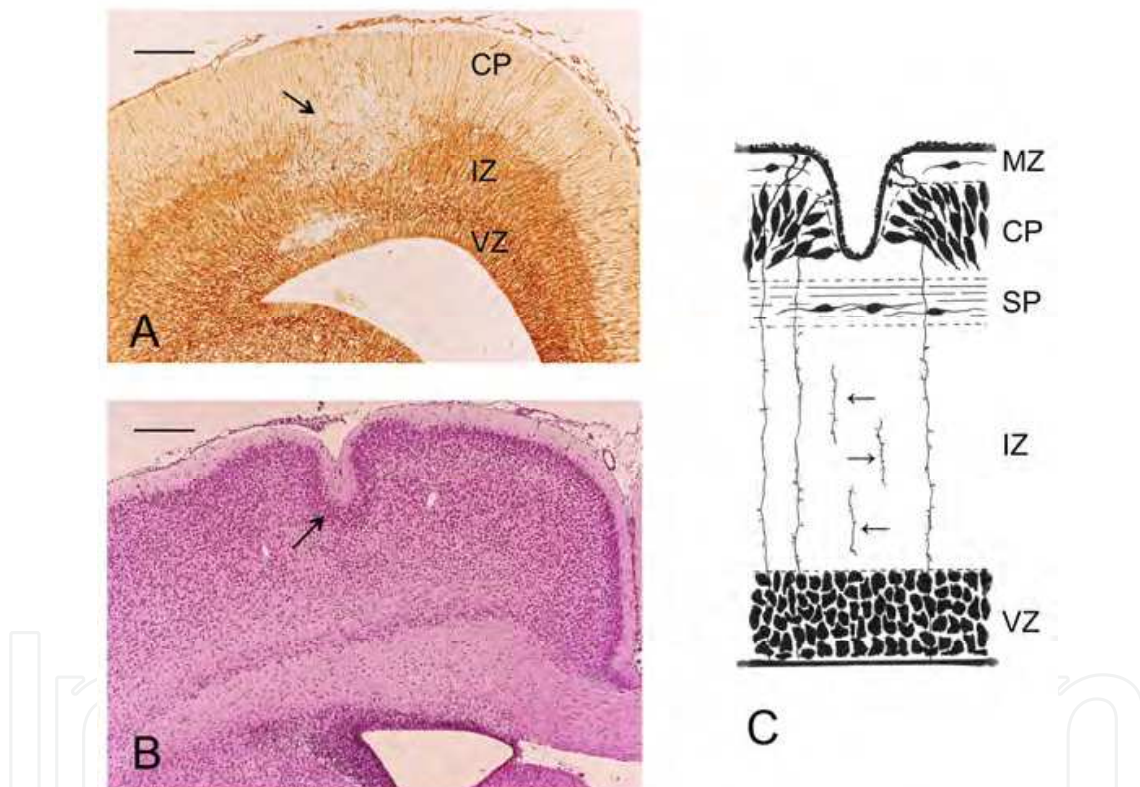


Fig. 1. A: Cortical lesions 1 day after ibotenate injection shown by vimentin immunohistochemistry. Note the disrupted neuronal arrangement in the cortical plate and intermediate zone, lacking the vimentin-positive radial glial fibers (arrow). B: Cortical infolding mimicking microgyria (arrow) 5 days after ibotenate injection. Hematoxylin-eosin staining. C: Cerebral cortex illustrating the histogenetic development of the microgyria. After the radial glial fibers were damaged (small arrows), its corresponding area within the cortical plate collapsed. As the surrounding neurons migrate along the radial fibers, the cortical plates roll in and infold. MZ, marginal zone; CP, cortical plate; SP, subplate; IZ, intermediate zone; VZ, ventricular zone. Scale bar, A = 120 μm , B = 160 μm . Modified from Takano T, et al. (2005)

3. Congenital bilateral perisylvian syndrome and epilepsy

Several specific syndromes are associated with cerebral polymicrogyria. Congenital bilateral perisylvian syndrome (CBPS) was first described by Kuzniecky and coworkers (1993), and it is characterized by pseudobulbar palsy, cognitive deficits, and bilateral perisylvian abnormalities such as polymicrogyria (Table 1). Pseudobulbar palsy is one of the striking clinical symptoms of CBPS, however, the oropharyngoglossal dysfunction, such as abnormal tongue movement and the presence of dysarthric speech, may be difficult to investigate in young children. Moreover, epilepsy is an additional diagnostic manifestation of this syndrome, but the mean age at seizure onset has been estimated to be 7.9 years (Kuzniecky et al., 1994). Therefore, in the pediatric population, CBPS is likely to have different manifestations than in adults (Gropman et al., 1997).

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|---|
| <p>Essential criteria (present in 100% of cases)</p> <ul style="list-style-type: none"> Oropharyngoglossal dysfunction Moderate to severe dysarthria Bilateral perisylvian malformations on imaging |
| <p>Additional criteria (present in > 85% of cases)</p> <ul style="list-style-type: none"> Delayed milestones Epilepsy (usually atypical absence and atonic seizures) Mental retardation Abnormal EEG |
| <p>Other criteria (present in \leq 50% of cases)</p> <ul style="list-style-type: none"> Arthrogryposis multiplex Other limb malformations Infantile spasms |

Table 1. Criteria for the diagnosis of congenital bilateral perisylvian syndrome (CBPS) (Kuzniecky R, et al. (1993))

Three cases of epilepsy with congenital bilateral or unilateral perisylvian polymicrogyria are presented as follows.

Case 1: This male child showed complex partial seizures (CPS) at 3 years of age. Electroencephalogram (EEG) revealed focal spikes on the bilateral frontal areas, and carbamazepine (CBZ) was started. No feeding difficulties and drooling were observed, but expressive language development was mildly delayed. Brain computed tomography (CT) was not able to reveal the cortical abnormalities at 3 years of age. His epileptic seizures were well-controlled by the administration of CBZ, but CPS reappeared due to withdrawal at 16 years of age. Brain magnetic resonance imaging (MRI) showed narrow and deep sylvian fissures and their surrounding pachygyric cortex on fluid-attenuated inversion-recovery

(FLAIR) image (Figure 2A). Although no pseudobulbar disorders have yet been recognized, his expressive language skills have been still delayed, and he was diagnosed to have pervasive developmental disorders.

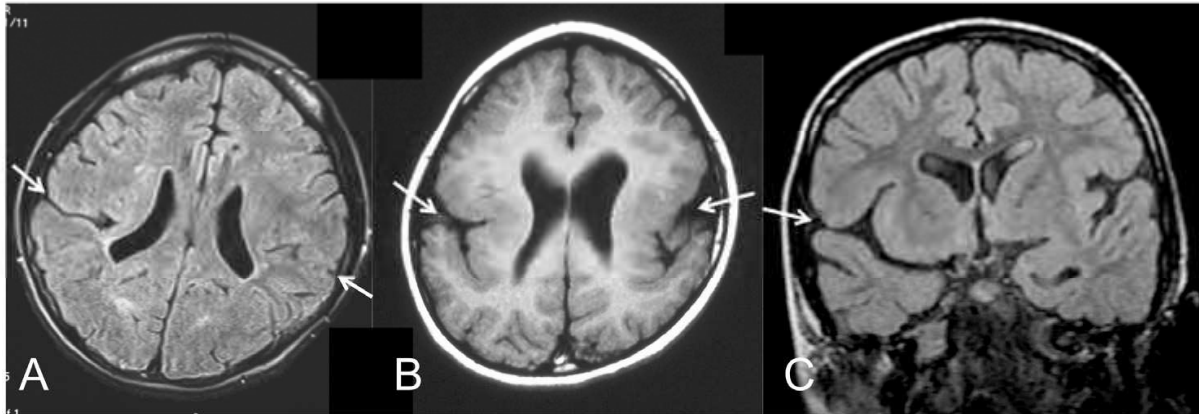


Fig. 2. Brain magnetic resonance imaging (MRI) findings of three patients with perisylvian polymicrogyria. Fluid-attenuated inversion-recovery (TR/TE/ TI = 8002/133/2000 ms) (A, C), and T1-weighted MRI (TR/TE = 500/9 ms) (B). A: Case 1. Narrow and deep sylvian fissures (arrows) and their surrounding pachygyric cortex were found. B: Case 2. The bilateral perisylvian cortical dysplasia are accompanied with bilateral dysplastic insula (arrows). C: Case 3. Note the dysplastic right perisylvian cortex with broad and thickened gyri (arrow).

Modified from Takano T, et al. (2010)

Case 2: This male child was referred to our hospital because of epileptic seizures which he suffered at 12 years of age. His school performance was normal, and he has not shown any developmental abnormalities and pseudobulbar disorders. His seizure type was CPS, which included behavioral arrest, lateralized tonic posturing with head and eye deviation, and facial automatisms. Interictal EEG showed focal spikes on the left front-temporal area. These clinical findings suggested a diagnosis of temporal lobe epilepsy. Brain MRI revealed bilateral perisylvian cortical dysplasia, accompanying with an abnormality of the insula and of the parietal cortex on T1-weighted image (Figure 2B). The frequency of his epileptic seizures was monthly, and partial or transitory improvements have been obtained with CBZ, zonisamide or phenytoin.

Case 3: This female child manifested generalized tonic-clonic seizures or left partial seizures during sleep at 4 years of age. Her psychomotor development was mildly delayed, accompanied with mild left hemiparesis. Initial EEG showed focal slow spikes with frequent associated diffuse slow spikes and waves. In brain MRI, the right perisylvian cortex was dysplastic showing the appearance of pachygyria with broad and thickened gyri, suggesting right perisylvian polymicrogyria (Figure 2C). Her generalized or partial seizures were refractory to the administration of valproate or CBZ, respectively. Four months later, her sleep EEG demonstrated continuous bilateral and diffuse slow spike and waves, mainly at 1.5 ~ 2.5 Hz, persisting through all the slow sleep stages (Figure 3). These characteristic clinical features were considered as the diagnosis of the epilepsy with continuous spikes and waves during slow sleep.

More immature anomalous brain lesions may be associated with an enhanced capacity for epilepsy and resultant refractory seizures (Takano et al., 2006). However, the epilepsy

related to polymicrogyria may have variable types and severity, including cases with good outcome and spontaneous remissions, even after a period of intractability. Surgical treatment of epilepsy may be applicable to a very limited number of patients in whom large resections are feasible, because the epileptogenic zone in polymicrogyria remains largely unknown.



Fig. 3. Sleep EEG of Case 3. Note the continuous bilateral and diffuse slow spike and waves.

4. Epileptogenicity in experimental polymicrogyria by freeze lesion model

Polymicrogyria can be modeled in rats with a transcortical prenatal or neonatal freeze lesion, which mimics the histological characteristics of a human four-layered polymicrogyria. This experimental model does not have spontaneous epileptiform activity *in vivo*, but several investigations have been presented concerning the epileptogenicity of this malformation.

4.1 Upregulation of glutamate receptor subunits

Glutamate receptors are widespread in the nervous system where they are responsible for mediating the vast majority of excitatory synaptic transmission in the brain and spinal cord. The glutamate receptor family is composed of several distinct subtypes, which are pharmacologically distinguished by four agonists: NMDA, amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA), kainate, and quisqualate. Electrical kindling stimulation in prenatal freeze lesion rat revealed the significant prolonged after discharges in both of the cortex and hippocampus, the early development of hippocampal kindling,

and the spontaneous cortico-hippocampal spikes. Immunoreactive expression for NMDA receptor subunit 1 and 2B was shown to be markedly upregulated not only in the microgyria, but also in the hippocampus (Takase et al., 2008). These investigations indicate that dysplastic cortex of microgyria can be highly seizure susceptible lesion by a certain brain insult such as kindling or excitable cortical stimulation.

4.2 Alterations in ion channels

Na⁺, K⁺-ATPase contributes to the asymmetrical distribution of sodium and potassium ions across the plasma membrane and to maintenance of the membrane potential in many types of cells (McGrail et al., 1991). A decrease in $\alpha 3$ subunit expression may cause neurons to be less effective in restoring their normal electrochemical gradient and membrane potential after repeated membrane depolarization, resulting in hyperexcitability (Li & Stys, 2001; Vaillend et al., 2002). Alterations in this protein are thought to play a significant role in many human neurological disorders, including epilepsy. It has been demonstrated that there was a significant decrease in $\alpha 3$ subunit of Na⁺, K⁺-ATPase immunoreactivity in the neuropil of freeze lesion cortical layer V in paramicrogyral area, where is an area that typically exhibits evoked epileptiform activity. The significant decrease in Na⁺, K⁺-ATPase in the paramicrogyral cortex is suggested to contribute to epileptogenesis (Chu et al., 2009).

4.3 New excitatory or inhibitory rewiring

The electrophysiological studies by cortical slices demonstrated that the field potentials evoked by stimulation within a few millimeters of the microgyrus have characteristics typical of epileptiform activity. These results imply that the epileptiform activity in polymicrogyria can be generated outside the lesion itself, which is a focal zone adjacent to the microgyria and called paramicrogyral area (Jacobs et al., 1996; Jacobs et al., 1999). Jacobs and Prince (2005) recorded isolated whole cell excitatory postsynaptic currents (EPSCs) and GABA_A receptor-mediated inhibitory postsynaptic currents (IPSCs) from layer V pyramidal neurons in the region of paramicrogyral area. They demonstrated that the conductance or the frequency of IPSCs or EPSCs was significantly larger or greater in paramicrogyral cells compared with controls. These findings imply that there is an increase in numbers of functional excitatory synapses on both interneurons and pyramidal cells in the paramicrogyral cortex, because the cortical afferents unable to find appropriate targets within the malformed region may instead synapse in the adjacent paramicrogyral area.

4.4 Downregulation of GABA_A receptor subunits

Synaptic inhibition in the mammalian brain is mediated principally by γ -aminobutyric acid (GABA) receptors. The most widespread ionotropic receptor activated by GABA is designated GABA_A. The majority of GABA_A receptors contain a variable combination of α , β , and γ subunits, showing a specific regional and cellular distribution (Fritschy & Mohler, 1995). Functional studies demonstrated that the subunit composition of receptor subtypes determines their electrophysiological and pharmacological properties (Barnard et al., 1998; Narahashi, 1999). In adult rats with freeze-lesioned microgyria, widespread regionally differential reduction of GABA_A receptor subunits $\alpha 1$, $\alpha 2$, $\alpha 3$, $\alpha 5$, and $\gamma 2$ was observed within the microgyral area and the lateral to the dysplastic cortex. It has been also observed that the downregulation of GABA_A receptor subunits involved the ipsilateral hippocampal formation, as well as restricted contralateral neocortical areas, indicating widespread

disturbances in the neocortical and hippocampal network (Redecker et al., 2000). The downregulation of GABA_A receptor subunits might contribute to the widespread cortical hyperexcitability in patients with polymicrogyria.

5. Interneurons and epileptogenicity of polymicrogyria

The proper functioning of the cerebral cortex is dependent on two classes of neurons: a) excitatory, projecting neurons, with pyramidal somatodendritic morphology using glutamate as a neurotransmitter, which typically send their axons to distant cortical as well as subcortical targets; b) inhibitory local circuit interneurons, whose axonal arborization is typically restricted to the neocortex and does not project into the white matter (Druga, 2009). These neurons primarily use GABA as a neurotransmitter. The majority of cortical neurons belong to the category of pyramidal cells. Cortical GABAergic interneurons represent about 20-30% of the total number of neocortical neurons (Druga, 2009).

We previously demonstrated the intracerebral injection of ibotenate produces excitotoxic brain lesions to mimic neuronal migration disorders (Takano et al., 2004). We also reported that subventricular zone cells play an important role in the formation of cortical dysplasia (Sawai et al., 2009). Biotinylated dextran amine (BDA) are highly sensitive tools for anterograde and retrograde pathway tracing studies of the nervous system. The high molecular-weight BDA yields sensitive and exquisitely detailed labeling of axons and terminals using preferentially anterograde transport. In the brains injected with BDA to the ganglionic eminence, BDA-positive fibers were derived from the dorsolateral part of the subventricular zone (Figure 4A), and BDA-labeled neurons were specifically located within

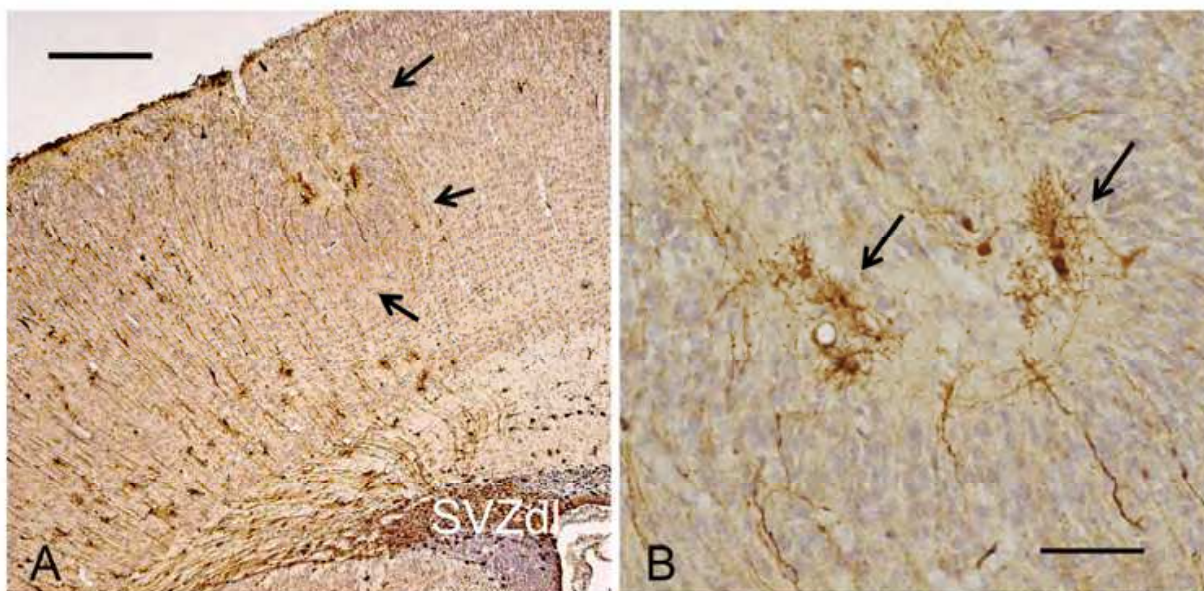


Fig. 4. Biotinylated dextran amine (BDA) tracer immunohistochemistry with hematoxylin double staining 5 days after ibotenate injection. A: Numerous BDA-positive radially oriented fibers extended from the dorsolateral part of the subventricular zone (SVZdl) and reached the pial surface in the frontoparietal cortex. Note the microgyria (arrows). B: Higher magnification of microgyria in A. Note the BDA-positive neurons in the microgyric cortex (arrows), which were mobilized out of the ganglionic eminence. Scale bar, A = 120 μ m, B = 80 μ m.

the polymicrogyric area of the parietal cortex (Figure 4B). This experiment demonstrated that the interneurons are mobilized to the microgyric area out of the ganglionic eminence, which thus leads to the construction of a part of the abnormal neuronal arrangement of this microgyria (Takano et al., 2010). Polymicrogyria is not invariably associated with epilepsy, and the pathogenetic basis of epileptogenesis in polymicrogyria is also unclear. It is suggested that one of the factors that might explain why some patients with polymicrogyria do not develop epilepsy may be due to the fact that a population of aberrantly migrating inhibitory interneurons are present in the microgyric area.

6. Conclusion

The cortical hyperexcitability in polymicrogyria may be reduced by the inhibitory neuronal network constructed by a population of aberrantly migrating inhibitory interneurons, which are mobilized from the ganglionic eminence during the development of polymicrogyria.

7. Acknowledgment

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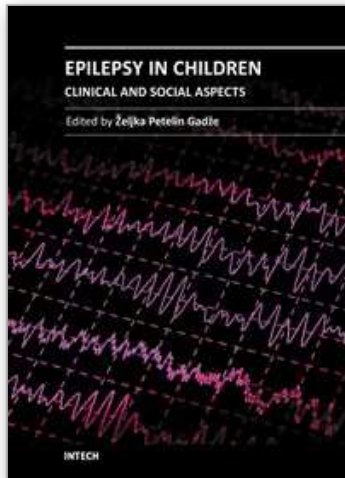
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Epilepsy is a neurological condition that accompanies mankind probably since its inception. About 400 years before Christ, the disease was already known by Hippocrates, who wrote the book "On The Sacred Disease". Classically, epilepsy has been defined as a chronic condition characterized by an enduring propensity to generate seizures, which are paroxysmal occurring episodes of abnormal excessive or synchronous neuronal activity in the brain. Out of all brain disorders, epilepsy is the one that offers a unique opportunity to understand normal brain functions as derived from excessive dysfunction of neuronal circuits, because the symptoms of epileptic seizures are not the result of usual loss of function that accompanies many disease that affect the brain. I am therefore extremely honoured to present this book. The 15 very interesting chapters of the book cover various fields in epileptology – they encompass the etiology and pathogenesis of the disease, clinical presentation with special attention to the epileptic syndromes of childhood, principles of medical management, surgical approaches, as well as social aspects of the disease.

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