Clinical characteristics in patients with hippocampal sclerosis with or without cortical dysplasia

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ABSTRACT – Background. Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) constitutes a distinct clinical syndrome with variable pathogenesis. Extrahippocampal regions may be affected in MTLE/HS, association with cortical dysplasia is common and temporal polar cortex is frequently involved in seizure onset. Patients with dual pathology may have favourable outcome from the surgery provided that both pathologies are removed. The aim of the study was to review clinical variables of MTLE/HS patients in order to distinguish preoperatively patients with associated microscopic cortical dysplasia in the temporal pole.

Methods. A series of 38 patients with the clinical diagnosis of MTLE and histopathologically proven HS were analysed. Patients were divided into two groups on the basis of histopathological finding in the temporal polar cortex: HS associated with malformation of cortical development (group HS+, n = 19) and a group with isolated HS (group HS, n = 19). Demographic, clinical, electrographic and seizure semiology variables were obtained and their prevalence compared between both groups.

Results. At least one insult was identified in early childhood history of 18 patients in the HS group in comparison to 10 patients in the HS+ group (p < 0.01). Complicated febrile seizures were found in both groups with similar prevalence, the history of early childhood CNS infection prevailed in the HS group (p < 0.01). Absence of aura was reported in HS group only. Patients in the HS+ group had earlier surgery (p < 0.05) but the seizure outcome was comparable between groups.

Conclusions. Microscopic dual pathology is common in MTLE/HS patients. This group of patients is difficult to distinguish preoperatively on the basis of noninvasive electrographic features or ictal clinical semiology. Detailed information regarding the possible precipitating insult in the history may be of critical importance.

Key words: epilepsy, hippocampal sclerosis, cortical dysplasia, initial injury
Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis (HS) has been recently defined as a distinct clinical syndrome; however, etiological and pathological factors of this condition are still controversial (Wieser 2004). Extrahippocampal histological, morphological and metabolic changes have been described in patients with HS and the temporal pole is one of the areas frequently affected (Choi et al. 1999; Mitchell et al. 1999; Diehl et al. 2003). Temporal polar cortex is involved at the onset of seizures in about 35% of cases of temporal lobe epilepsy with HS (Chabardes et al. 2005).

The presence of cortical dysplasia in patients who underwent temporal lobectomy was first described by Taylor et al. (1971). Since then, an association of hippocampal sclerosis with macroscopic or microscopic cortical dysplasia in the temporal lobe has been reported as a quite common pathology with dysplastic features found in the temporal neocortex in 10-50% of patients with hippocampal sclerosis (Raymond et al. 1994; Prayson et al. 1996; Kalnins et al. 2004; Fauser et al. 2006). Despite the improvement in various MRI techniques, the diagnosis of cortical dysplasia remains a pathologic one in approximately 25% of these patients (Li et al. 1995; Sisodiya 2000). Although this dual pathology of the temporal lobe is frequently observed in epilepsy patients, the clinical significance of the dysplastic tissue in the neocortical temporal lobe, in particular its epileptogenesis, for long time remained unclear (Raymond et al. 1994; Thom et al. 2001). Recent studies have suggested that dysplastic tissue in the temporal neocortex is often epileptogenic and the subtype of cortical dysplasia does not affect its relative contribution to seizure generation, i.e. even tissue with mild dysplastic features (mild malformation of cortical development [mMCD]) in the temporal neocortex could be epileptogenic (Fauser and Schulze-Bonhage 2006).

Patients with HS and associated cortical dysplasia are difficult to distinguish from the patients with isolated HS on the basis of general clinical features, MRI findings, or ictal clinical semiology. The clinical significance of temporal pole MRI abnormalities in temporal lobe epilepsy patients with hippocampal sclerosis is still unclear. Mild ipsilateral anterior temporal changes can be seen on MRI of a substantial number of patients and represent by some authors an abnormal persistent immature appearance, including an abnormality of myelin or myelination (Mitchell et al. 1999; Mitchell et al. 2003), by others these changes may be associated with cortical dysplasia (Kuzniecky et al. 1987; Ho et al. 1998). MRI volumetric and PET studies have found group differences between patients with isolated HS and HS associated with cortical dysplasia. The presence of bilateral temporal lobe atrophy is suggestive of a more widespread (bilateral) temporal lobe involvement in patients with HS and cortical dysplasia (Diehl et al. 2004) and in patients with isolated HS, the most prominent hypometabolism was in the anterior and mesial temporal lobe, whereas in dual pathology, it was in the lateral temporal lobe (Diehl et al. 2003). However, these group differences may not distinguish associated cortical dysplasia preoperatively in individual patient. Reports on the postoperative outcome of patients with dual pathology are controversial. Early studies reported that patients with HS and associated microscopic cortical dysplasia have a higher risk for seizure recurrences after epilepsy surgery as compared with patients with only HS (Palmini et al. 1994). More recent investigations, however, demonstrates that these patients can have a very favourable outcome provided that both pathologies were removed (Thom et al. 2001; Srikijvilaikul et al. 2003; Fauser et al. 2004; Kalnins et al. 2004). Therefore, the distinction between this group of patients and those with isolated HS is important and may assist in the presurgical diagnosis and improve the postoperative seizure outcome.

**Materials and methods**

**Subjects**

Thirty-eight patients with refractory MTLE/HS who underwent anteromedial temporal lobe resection comprising the removal of the mesial and the adjacent anterior neocortical structures were studied. Pre-operative evaluation was done in the Epilepsy Centre at the University Hospital Motol in Prague using a noninvasive protocol (neurologic history/examination, routine EEG, long-term video-EEG monitoring, an epilepsy protocol MRI, neuropsychological testing and bilateral carotid sodium amobarbital/methohexital testing, intraoperative electrocorticography), moreover invasive video-EEG was performed in two patients. In each case MRI showed on visual analysis hippocampal atrophy or signal increase on T2-weighted and FLAIR images on the side of resection and the diagnosis of HS with or without malformation of cortical development was histopathologically confirmed. All patients had at least two years of clinical follow-up.

**Clinical and demographic details**

The patients’ clinical and demographic variables were determined by retrospective review of the medical records (table 1). The following variables were collected: sex, age at surgery, history of early childhood (age less than 4 years) brain injury (e.g. birth trauma, head trauma, meningitis or encephalitis), complicated febrile seizures (lateralised and/or prolonged), neurological examination, handedness, age at onset of habitual afebrile seizures, presence of auras, generalised tonic-clonic seizures reported in the history and seizure frequency. The history of simple febrile seizures was obtained, but these were not considered as possible initial precipitating injury (table 2).
Table 1. Demographic data, clinical, electrographic and histopathological characteristics and outcome.

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FS = febrile seizure; CFS = complicated FS; M = meningitis; E = encephalitis; ME = meningo-encephalitis; P = perinatal (birth) trauma; T = trauma; epig = epigastric (abdominal) aura; auton = autonomic aura; OAA = oroalimentary automatisms; Sz = seizure; ipsi = ipsilateral to the epileptogenic zone; bilat = bilateral; mMCD I,II = mild MCD type I, II; FCD IA,IB = focal cortical dysplasia type IA, IB; N = normal finding; gli = gliosis; * = in patient 2 history until the age of one year not available.
Interictal, ictal EEG and seizure semiology

The interictal EEG was assessed with respect to ipsilateral or bilateral occurrence of spikes/sharp waves over the anterotemporal region and/or in the sphenoidal electrode. The spikes were considered bilateral if more than 10% of the total spike count was observed contralaterally. On the basis of seizures recorded during preoperative video-EEG monitoring, semiology and ictal EEG were reviewed for the occurrence of the features listed in Table 3. Seizure onset was defined as the time when the patient indicated a warning (e.g. pushing a button); or from the first evidence of abnormal movement or altered responsiveness (if no warning); or as the first appearance of electrographic ictal pattern if EEG changes preceded the clinical signs. In the ictal EEG, rhythmic 4-8 Hz (theta) activity was assessed as “early” if present within 20 seconds from the seizure onset. The seizure pattern was considered “bilateral” if rhythmic theta was seen bilateral at the onset of the seizure or if independent seizures arising from both temporal lobes were recorded.

Seizure types were classified according to the semiological seizure classification (Luders et al. 1998). Auras were considered if reported by the patient at least in some of the seizures recorded in video-EEG and/or clearly reported in the history. Oroalimentary automatisms were classified as “early” when described at least in one seizure within 20 seconds from the seizure onset. Possible lateralizing signs (contralateral ictal dystonia, ictal speech, postictal aphasia or hemiparesis) were noted if present at least in one seizure. The spread of the seizure to the frontal lobe or to the contralateral temporal lobe was assessed on the basis of EEG and semiology evolution.

Table 2. Demographic and clinical characteristics of the total cohort and comparison of HS and HS+ groups.

<table>
<thead>
<tr>
<th></th>
<th>MTLE/HS (n = 38)</th>
<th>HS+ (n = 19)</th>
<th>HS (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>18/20</td>
<td>8/11</td>
<td>10/9</td>
</tr>
<tr>
<td>Age at surgery (yrs)</td>
<td>26.9</td>
<td>23.2</td>
<td>30.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Simple febrile seizures</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Initial precipitating injury</td>
<td>28</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>– Perinatal (birth) trauma</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>– Complicated febrile seizures</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>– CNS infection</td>
<td>13</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>Epilepsy onset (yrs)</td>
<td>9.4</td>
<td>8.9</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Epilepsy duration (yrs)</td>
<td>17.5</td>
<td>14.3</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Seizure frequency (per month)</td>
<td>14.0</td>
<td>17.8</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>GTCS in history</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

HS group = group with isolated hippocampal sclerosis; HS+ group = group with hippocampal sclerosis associated with malformation of cortical development; Complicated febrile seizures = lateralized, prolonged or in cluster; GTCS = generalized tonic-clonic seizure; ns = not significant.

Table 3. Electrographic and seizure characteristics of the total cohort and comparison of HS and HS+ groups.

<table>
<thead>
<tr>
<th></th>
<th>MTLE/HS (n = 38)</th>
<th>HS+ (n = 19)</th>
<th>HS (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric aura</td>
<td>22</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Psychic aura</td>
<td>6</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Absence of aura</td>
<td>5</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Early OAA</td>
<td>33</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Ictal contralateral dystonia</td>
<td>12</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Ictal speech</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Postictal lateralization</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Bilateral IED</td>
<td>11</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
<tr>
<td>Early ictal rhythmical theta</td>
<td>20</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

HS group = group with isolated hippocampal sclerosis; HS+ group = group with hippocampal sclerosis associated with malformation of cortical development; Early OAA = oroalimentary automatisms observed in less than 20 seconds from seizure onset; Ictal dystonia = ictal dystonic posturing of contralateral upper extremity; Postictal lateralization = postictal hemiparesis or aphasia; GTCS = generalized tonic-clonic seizure; Bilateral IED = bilateral interictal epileptiform discharges, i.e., more than 10% of contralateral spikes; Early ictal rhythmical theta = appearance of the pattern in less than 20 seconds from seizure onset; ns = not significant.
Histopathology
Pathologic specimens from all patients were obtained (right: 13, left: 25). Resected tissue (hippocampus and temporal neocortex) was fixed in 10% buffered formalin, and topographically oriented samples were embedded in paraffin. To determine the histopathological features of the specimen, routine hematoxylin-eosin and cresyl violet staining was performed on 4 μm thick sections from all the paraffin blocks. Diagnosis of HS was based on cell counts performed by an experienced observer who was blinded to the EEG, clinical, and MRI data. HS was defined as average cell loss of at least 30% in the CA1 and CA4 subfields. In each patient the temporal neocortical samples were examined and assessed as non-malformed (HS group) or presenting signs of MCD (HS+ group). The presence of MCD in the adjacent temporal neocortex qualified for the inclusion in the dual pathology group. Samples presenting MCD were classified according to the recommendation of the recent classification of cortical dysplasias (Palmini et al. 2004). Histopathological findings indicating any previous CNS affection, e.g. post-inflammatory or post-traumatic changes, were searched in both non-malformed and dysplastic temporal neocortex.

Postoperative follow-up
Surgical outcome with respect to seizures was assessed according to a modified Engel classification (Wieser et al. 2001). Patients with a class 1a outcome were considered as having had an excellent outcome, and those with a class 1 or class 2 outcome as having had favourable outcome. Outcome was assessed at the latest follow-up.

Statistical methods
Fisher’s exact test (two-tailed) was used to test for differences between the groups (HS and HS+) for dichotomous variables. The Mann–Whitney U test (two-tailed) was used for continuous or ordinal variables. P values < 0.05 were regarded as statistically significant.

Results
Isolated HS was histopathologically confirmed in 19 patients (HS group), and associated MCD was seen in other 19 patients (HS+ group).

Clinical and demographic details
Results of the total group and comparison between HS and HS+ groups are given in table 2. As shown, the age of epilepsy onset did not differ between groups, but mean age at surgery was lower and the duration of epilepsy shorter in HS+ group in comparison to HS group (p < 0.05). History of possible initial precipitating injury (IPI) in early childhood was much frequent in the isolated HS group (in all the patients except one). The IPI history was not reported in 9 patients of the HS+ group (p < 0.01). Prevalence of inflammatory CNS affection was much more higher in isolated HS group (p < 0.01). The prevalence of complicated febrile seizures was comparable in patients with isolated HS and HS associated with MCD. The same held true for the prevalence of uncomplicated febrile seizures. Seizure frequency ranged from one to one hundred per month and showed a trend to a higher frequency in HS+ group. Secondary generalization was reported in 79% patients of the entire cohort with similar prevalence in both groups. There were no significant differences between the two groups with respect to the results of neurological examination or handedness.

Interictal, ictal EEG and seizure semiology
Results of the total group and comparison between the patients in HS and HS+ groups are given in table 3. The majority of interictal epileptiform activity was arising from the ipsilateral temporal lobe; bilateral interictal spikes were found in five of the patients with HS and in six of the patients with HS+.

Histopathology
MCD in neocortex (HS+ group)
The samples classified as “mild MCD” (n = 5) were characterized by the presence of ectopically placed neurons in or adjacent to layer I (type I, n = 3) or by microscopic neuronal heterotopia outside layer I (type II, n = 2). In addition to changes seen in the “mild MCD” group, the cresyl violet staining of samples of FCD type I (n = 14) revealed dyslamination and columnar disorganization without (type IA, n = 9) or with giant pyramidal-shaped neurons and/or round immature neurons with a large nucleus and a thin rim of cytoplasm (type IB, n = 5). There was no patient with FCD type II in this study. In one patient the finding of FCD type IB and post-inflammatory changes coincided in neocortical specimen.

Non-malformed neocortex (HS group)
In patients without associated MCD in the neocortex the histopathological examination revealed post-inflam-
tory changes, *i.e.* focal gliosis in the cerebral cortex accompanied by mild lymphocytic perivascular cuffs with or without meningeal fibrosis (*n* = 9), post-traumatic changes, *i.e.* focal gliosis and hemosiderin deposition (*n* = 1) or normal findings (*n* = 9).

**Side of surgery and postoperative outcome**

In 25 cases left-sided surgery was performed, in 13 cases right-sided. In the HS+ group the number of left-sided patients prevailed, but the difference between the two groups was not statistically significant. The postoperative follow-up ranged from 2.7 to 7.1 years, with a mean of 4 years and 2 months. Overall, 55% of patients (21/38) were seizure and aura free (Engel 1a). Another 26% (10/38) had a favorable outcome (Engel 1 or 2). According to histopathologic findings 89% of patients with isolated HS had a favorable outcome compared to 74% of HS+ patients.

In comparison between the group of patients with excellent (Engel 1a) outcome and the group of other patients, the duration of epilepsy did not correlate with outcome but patients with a lower age at surgery had a higher chance of excellent outcome. Only three patients (14%) had bilateral interictal spikes in the group with excellent outcome in the contrast to eight patients (47%) in the other group (*p* < 0.05).

**Discussion**

In the present study we found an associated MCD in half of the MTLE/HS patients. This is in agreement with previous studies (Raymond et al. 1994; Prayson et al. 1996; Diehl et al. 2004; Kalnins et al. 2004). A relatively higher number of microscopic dual pathology cases in our study may be explained by inclusion of paediatric patients in the cohort – associated MCD has been reported to be more frequent in this population (Mohamed et al. 2001).

**Clinical and demographic details**

The occurrence of initial precipitating injury (IPI) and the prevalence of different IPI types was the most striking difference between HS and HS+ groups. Nearly half of the MTLE/HS patients with associated MCD had no IPI in early childhood, whereas all patients with isolated HS except one had such an insult reported. We did not consider simple FS to be a possible IPI, as they present no significant risk for development of temporal lobe epilepsy (Lee et al. 1981). Complicated FS are frequently referred as one of the most frequent IPI preceding the development of HS, but some authors also report FS as the consequence of a developmental lesion of the hippocampus or the temporal lobe (Annegers et al. 1987; Raymond et al. 1994). In agreement with both theories we observed similar prevalence of complicated FS in both groups. The history of early childhood intracranial infection seems to be the most sensitive IPI in our series that could distinguish between both groups. The history of meningitis and/or encephalitis was reported in 11 patients with isolated HS and in only two patients of the HS+ group. Other studies have also not found the coincidence of CNS infection and MCD in patients with MTLE. (Davies et al. 1996; Lee et al. 1997).

In a recent study (Bautista et al. 2003), CNS infection was reported frequently in patients with dual pathology, but the data were not confirmed by histopathological findings of post-inflammatory changes as in our cohort of patients. The lower age at surgery and shorter duration of epilepsy in the HS+ group may be due to tendency of the patients to suffer from more frequent seizures.

**Seizure semiology, interictal and ictal EEG**

Dysplastic cortex in the temporopolar region is often epileptogenic, and this has been reported also in the cases when MCD is associated with HS (Fauser and Schulze-Bonhage 2006).

Without help of depth electrodes, mesiotemporopolar seizures are not to be easily distinguished from mesiotemporal seizures on the basis of their electro-clinical characteristics (Chabardes et al. 2005). In agreement with these findings, similar ictal and interictal electro-clinical characteristics in patients from both groups have been observed in the present study. Seizure semiology was typical mesiotemporal in most patients and the prevalence of typical auras and oroalimentary automatisms similar to previously reported data (O’Brien et al. 1996; Pfander et al. 2002). The absence of aura in five patients of the HS group is an interesting finding that should be taken cautiously as only relatively small number of patients presented this finding.

Early rhythmic theta was recorded as an ictal EEG pattern in substantial number of patients of the whole cohort, with similar prevalence as have been already described in other studies (Williamson et al. 1993; Foldvary et al. 2001). There was a trend for higher prevalence of this pattern in the group with isolated HS. This may be explained by a hypothetically higher proportion of seizures arising from the temporal pole in the group with associated MCD (Fauser and Schulze-Bonhage 2006).

**Histopathology**

All spectrums of MCD were found in temporal pole specimen of HS+ group, except for FCD type II. Although there were few patients with MTLE/HS and FCD type II identified in the database, they all showed clear temporal pole MRI abnormality and were not considered for this study. We included also patients with mild MCD into the cohort, as any type of cortical dysplasia could be epileptogenic (Fauser and Schulze-Bonhage 2006). The histopathological findings in non-malformed group revealed other types of pathology in the temporal pole; the most frequent ones were post-inflammatory changes. In all cases, except one,
Clinical characteristics of HS in patients with or without cortical dysplasia

a history of intracranial infection was reported. This finding coincided with MCD in only one case and was found in nearly half of the patients with isolated HS. This dichotomy and the absence of IPI in nearly half of the patients in the HS+ group support the idea that MTLE/HS is an etiopathogenetically heterogeneous syndrome caused by different developmental or acquired affections, isolated or in combination. In cases without initial precipitating injury and with dysplastic cortex in the temporal pole, repeated seizure propagation into the hippocampus may induce structural changes in the hippocampal architecture (Holmes et al. 1998; Huang et al. 1999). Complicated FS may be the only initial insult in some of the MTLE/HS patients, however, in other cases complicated FS probably occur on the basis of pre-existing MCD and may play a role as a second hit causing a more severe type of HS.

Outcome

The postoperative results with respect to seizures did not differ significantly between both groups. Patients with MCD may have as favourable outcome as patients with isolated HS. Because of potential epileptogenicity of microscopic MCD, dual pathology patients should be identified preoperatively and surgical approach modified on the basis of this information. When there is MCD present in the temporal pole, selective amygdalohippocampectomy may not be a sufficient procedure (Li et al. 1999). When planning anteromedial temporal lobe resection in a patient with presumed microscopic MCD in the temporal pole, the assessment of the extent of dysplastic cortex may be challenging. The invasive EEG study is an option but as the extent of the lesion is unknown the spatial sampling may not be sufficient. Intraoperative electrocorticography may be of help since typical interictal epileptiform discharges may be detected over the dysplastic cortex and included in surgical resection (Boonyapisit et al. 2003). Interictal epileptiform discharges extending beyond the area of resection correlate with poor surgical outcome in patients with extrahippocampal epilepsy (Bautista et al. 1999).

Conclusions

The microscopic MCD in temporal pole of MTLE/HS patients is difficult to be recognised preoperatively on the basis of noninvasive electrophoretic features or ictal clinical semiology. Detailed information regarding the possible precipitating insult may be of critical importance – absence of such an insult raises the possibility of associated MCD. On the contrary, history of early childhood intracranial infection seems to have a low chance to associate with malformation of cortical development.

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References


