The role of periventricular nodular heterotopia in epileptogenesis

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Summary
A temporal resection in patients with periventricular nodular heterotopia (PNH) and intractable focal seizures yields poor results. To define the role of heterotopic grey matter tissue in epileptogenesis and to improve outcome, we performed stereoencephalography (SEEG) recordings in eight patients with uni- or bilateral PNH and intractable focal epilepsy. The SEEG studies aimed to evaluate the most epileptogenic areas and included the allo- and neocortex and at least one nodule of grey matter. Interictal spiking activity was found in ectopic grey matter in three patients, in the cortex overlying the nodules in five and in the mesial temporal structures in all. At least one heterotopion was involved at seizure onset in six patients, synchronous with the overlying neocortex or ipsilateral hippocampus. Two patients had their seizures originating in the mesial temporal structures only. Six patients had surgery and the resected areas included the seizure onset, with follow-up from 1 to 8 years. An amygdalo-hippocampectomy was performed in two (Engel class Ia and III), an amygdalo-hippocampectomy plus removal of an adjacent heterotopion in two (class Ia), and a resection of two contiguous nodules plus a small rim of overlying occipital cortex in one patient (class Ia). One patient with bilateral PNH had three adjacent nodules resected and an ipsilateral amygdalo-hippocampectomy resulting in a reduction of the number of seizures by 25–50%. The best predictor of surgical outcome is the presence of a focal epileptic generator; this generator may or may not include the PNH. Invasive recording is required in patients with PNH; it improves localization and is the key to better outcome.

Keywords: periventricular heterotopia; epileptogenesis; electroencephalography; MRI; seizure

Abbreviations: IEA = interictal epileptiform activity; PNH = periventricular nodular heterotopia; SEEG = stereoencephalography

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Introduction
Periventricular nodular heterotopia (PNH) are a well-defined pathological entity among migrational neuronal disorders characterized by aggregates or masses of grey matter adjacent to the lateral ventricular walls just beneath and abutting the ependyma (Friede, 1989; Barkovich and Kjos, 1992; Raymond et al., 1994). They probably result from an arrest in the migrational progress of neuroblasts from the periventricular layer to the cortex, which usually occurs maximally between the 7th and 16th gestational weeks, along radial glial fibres (Rakic, 1978, 1985, 1995; Sarnat, 1991), or are due to a failure of programmed cell death of groups of neuroblasts within the periventricular germinal matrix (Kuida et al., 1996).

The pathogenic mechanisms of grey matter heterotopia are not fully understood, but they lead to distinct clinico-radiological syndromes and genetic characteristics that have been described recently (Barkovich and Kuzniecky, 2000). Subependymal or periventricular heterotopia are the most commonly identified type of heterotopia in clinical practice (Barkovich and Kjos, 1992; Raymond et al., 1994; Dubeau et al., 1995; Li et al., 1997).
The prevalence of PNH in patients with epilepsy is unknown. While most patients reported in the literature have had refractory seizures, this may represent a referral bias, and some individuals (~20%) have no seizures (Dubeau et al., 1995). The associated epilepsy syndrome is variable and seizures may be generalized or focal, often suggesting mesial or neocortical temporal and parieto-occipital onset (Raymond et al., 1994; Dubeau et al., 1997; Battaglia et al., 1997).

The clinical and electrophographic features of epilepsy in patients with PNH pointing to mesial temporal lobe origin are misleading, however. We demonstrated that resecting the temporal structures only in patients with PNH and intractable focal epilepsy usually led to unsatisfactory surgical results (Li et al., 1997). We previously proposed that PNH may either be the epileptogenic source or part of a more widespread epileptogenic network involving the hippocampus, and the overlying or distant neocortex. Very few electrophysiological studies recording directly from heterotopia were performed in humans (Morrell et al., 1992; Francione et al., 1994; Li et al., 1997; Preul et al., 1997; Kothare et al., 1998; Mai et al., 2003), and onset of seizures in the PNH was reported in an even smaller number of patients (Li et al., 1997; Preul et al., 1997).

In an attempt to clarify the role of PNH in epileptogenesis, we studied eight patients with PNH and medically intractable focal epilepsy who underwent intracranial stereoelectroencephalography (SEEG) evaluations exploring at least one PNH in addition to the adjacent and distant cortex and including the mesial temporal structures.

**Subjects and methods**

Since 1990 we evaluated >30 patients with PNH. The majority (80%) had seizures. Clinical and laboratory findings as well as surgical results in some were discussed in two previous publications (Dubeau et al., 1995; Li et al., 1997). Eight patients with PNH and pharmacologically resistant focal epilepsy underwent SEEG evaluation between February 1994 and May 2003 on the basis of intractable focal epilepsy. These patients were selected because they had particularly severe and disabling focal epileptic syndromes. Clinical, imaging and electrophysiological data are summarized in Table 1. Post-processing MRI analyses (Philips, 1.5 T) were performed in all subjects by one of us (D.K.), allowing evaluation of the shape and orientation of the hippocampi (Lehericy et al., 1995; Baulac et al., 1998), quantification of mesial temporal structures according to a protocol developed in our institution (Bernasconi et al., 2003) and better visual evaluation of the cortex (Bastos et al., 1995).

Three additional implanted patients followed at our institution were not included in this study, one because complications of the implantation confounded some of the electrophysiological results, and the other two because of the lack of adequate EEG information (these patients were implanted in the 1980s before we discovered the presence of bilateral occipital and trigonal PNH).

Depth and epidural electrodes were implanted stereotactically using an image guidance system (SSN Neuronavigation System Inc., Mississauga, Ontario, Canada). This is the only method that allows recording directly from the nodules. Intracerebral electrodes with nine contacts (each with a diameter of 0.5 mm), 5 mm apart, were placed in the lobe(s) suspected of containing the epileptic focus, in the adjacent or distant regions and in at least one heterotopy. Four patients had bilateral and four unilateral electrode implantations (Table 1). All had at least one temporal lobe evaluated with samples obtained from both mesial and neocortical structures. Four had in addition central or centroparietal electrodes, two had frontal leads and two had mesial and lateral occipital exploration. The number of nodules studied varied from one to six per patient. In seven patients, all MRI-determined nodules were explored (Fig. 1). In the remaining patient (patient 1) who had bilateral diffuse and contiguous PNH, only one electrode aimed to the frontal PNH. This case obviously showed definite sampling limitation. Epidual contacts were used in the majority of patients (n = 6) to improve surface neocortical sampling. In six patients, the exact positions of electrodes and recording contacts relative to the PNH and overlying cortex were verified by a post-implantation MRI (Fig. 2). One patient had a post-implantation temporal abscess without sequelae. Long-term video-SEEG recordings were performed (Harmonie Monitoring System, Stellate, Montréal, Canada) using 32 or 64 channels. Non-epileptiform activity and interictal and ictal (electro-clinical and pure electrographic seizures) epileptiform anomalies were analysed visually in all patients and in every structure explored. The epileptic focus was defined according to the results of the intracranial ictal recordings. Patients gave informed consent for their participation in this study according to the rules of the Montreal Neurological Institute and Hospital ethics committee.

**Results**

The eight patients (five men) had a mean age at evaluation of 34 years and at seizure onset of 12 years. All had a comprehensive investigation including clinical evaluation, classification of seizure semiology, routine and long-term scalp EEG recordings, high-resolution MRI studies and complete neuropsychological evaluation. Neurological examinations were unremarkable. On neuropsychological assessment, mean full-scale IQ was in the low borderline range at 84 (range 69–107) with uni- or bilateral diffuse cerebral dysfunction in five, temporal dysfunction in two, and temporo-parietal cognitive deficit in one.

**MRI findings and PNH distribution**

Patients showed variable distribution of the periventricular malformations along the lateral ventricles (Table 1 and Fig. 1). None had nodules along the third or fourth ventricles. Nodules were bilateral, diffuse and contiguous along both lateral ventricles in one (patient 1), bilateral focal in two (patients 6 and 8) and unilateral focal in the remaining five (patients 2, 3, 4, 5 and 7). One patient had in addition a parietal abnormal gyral pattern with subcortical heterotopia (patient 3), and another, closed-lip schizencephaly (patient 7). Six of eight patients had uni- or bilateral hippocampal atrophy, contralateral to the PNH in one (patient 2), and five had uni- or bilateral abnormal shape and positioning of the hippocampus (Table 1).
Seizure semiology and scalp EEG

Ictal semiology suggested temporal lobe seizure in five patients, posterior temporo-occipital in two and occipital in one. Scalp EEGs showed interictal epileptiform activity (IEA), synchronous or independent, predominating in the temporo-occipital regions in patients with bilateral diffuse and bilateral focal PNH (Table 1). It was ipsilateral \((n = 1)\) to the PNH or bilateral \((n = 4)\) in patients with unilateral focal PNH and maximal over temporal areas. Seizures were bilateral at onset in patients with bilateral diffuse or bilateral focal PNH, and unilateral at onset in those with unilateral focal PNH (in patient 2, onset was contralateral to the PNH), with maximal activity again over temporal areas.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex, age, onset (years)</th>
<th>MRI</th>
<th>Seizure type</th>
<th>Scalp EEG findings</th>
<th>SEEG interictal</th>
<th>SEEG ictal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F, 37, 13</td>
<td>Bil diffuse PNH, multiple, contiguous nodules; R Hc atrophy</td>
<td>No aura; oral and motor automatisms</td>
<td>ii: R CT, L T; i: bil CT</td>
<td>Bil Am and Hc, R&gt;L</td>
<td>85%: R Hc, 15%: Bil Hc</td>
</tr>
<tr>
<td>2</td>
<td>M, 43, 14</td>
<td>Uni PNH, one nodule, R trigone; L Hc and entorhinal atrophy</td>
<td>Visual aura; oral and motor automatisms, vocalizations</td>
<td>ii: bil T; i: bil T</td>
<td>Bil Am and Hc, L&gt;R</td>
<td>100%: L Am and Hc</td>
</tr>
<tr>
<td>3</td>
<td>M, 39, 19</td>
<td>Uni PNH, one nodule, R trigone; R P subcortical NH; R round Hc and thick subiculum</td>
<td>Auditory and epigastric aura; staring spells</td>
<td>ii: R T; i: R FT</td>
<td>R Am and Hc; R T neocortex; R supramarginal gyrus</td>
<td>100%: R Am, Hc and adjacent PNH</td>
</tr>
<tr>
<td>4</td>
<td>M, 31, 1</td>
<td>Uni PNH, 3 nodules, R trigone and T horn; bil Hc, ParaHc, Am, and entorhinal atrophy; bil round Hc, misplaced fimbria and thick subiculum</td>
<td>No aura; head to L, L arm posturing</td>
<td>ii: R T, bil FT; i: R T</td>
<td>R Am; R Hc and PNH</td>
<td>37%: R Am and cingulate gyrus 63%: R Hc and PNH (mostly EEG seizures)</td>
</tr>
<tr>
<td>5</td>
<td>M, 43, 13</td>
<td>Uni PNH, 2 nodules, L O horn; bil Hc, Am, and entorhinal atrophy; L round Hc, deep collateral sulcus, and thick subiculum</td>
<td>Visual and epigastric aura, fear; staring spells</td>
<td>ii: bil T; i: L TPO</td>
<td>L Lat O neocortex and PNH; L Am and Hc</td>
<td>100%: L lat O neocortex, PNH and post paraHc</td>
</tr>
<tr>
<td>6</td>
<td>F, 16, 5</td>
<td>Bil multiple nodules in both trigones and T O horns; R Hc atrophy; bil round and vertical Hc, paraHc and entorhinal atrophy, misplaced fimbria and thick subiculum</td>
<td>Visual aura, fear; head and eyes to L and staring spells</td>
<td>ii: bil TPO; i: bil TPO</td>
<td>Multifocal spiking in PNH, O T neocortex, and mesial T, R&gt;L</td>
<td>50%: Bil Hc, PNH and TO neocortex; 30%: R Hc, PNH and TO neocortex; 20%: L PNH and TO neocortex; several EEG seizures in L and R PNH, independent or synchronous with overlying neocortex 95%: R post T neocortex and adjacent PNH (26% clinical, 69% EEG seizure only) 5%: R Am (EEG seizures only)</td>
</tr>
<tr>
<td>7</td>
<td>F, 26, 16</td>
<td>Uni multiple PNH in R trigone and T horn; R post TP closed-lip schizencephaly</td>
<td>Feeling of head moving; staring spells, R arm and leg automatisms, oral automatisms, head to R</td>
<td>ii: bil T; i: R hem</td>
<td>R ant and post T neocortex; R Am and Hc</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>F, 38, 16</td>
<td>Bil PNH, 2 nodules in each trigone and O horn; L Hc and entorhinal atrophy; L round Hc and thick subiculum</td>
<td>Strange feeling; staring spells</td>
<td>ii: bil T; i: bil T</td>
<td>Bil TO neocortex; L Am and R Hc</td>
<td>30%: R TO neocortex; 30%: L TO neocortex; 40%: PNH only (EEG seizures)</td>
</tr>
</tbody>
</table>

Bil = bilateral, uni = unilateral, T= temporal, P = parietal, O = occipital, C = central, F = frontal, P = parietal, hem = hemispheric, R = right, L = left, Hc = hippocampus, Am = amygdala, PNH = periventricular nodular heterotopia, SH = subcortical heterotopia, ant = anterior, post = posterior, lat = lateral, ii = interictal, i = ictal.
Stereo-EEG findings, rationale for surgical approach and outcomes

Depth interictal and ictal EEG findings are summarized in Table 1, and extension of epileptogenesis, surgical approaches and outcomes in Table 2. Non-epileptiform EEG activity was analysed in the eight patients. We recorded different frequencies in the $\delta$, $\alpha$ and $\beta$ bands. The background activity recorded from the nodules was the same and synchronous with that recorded from the cortex, indicating probable connections between these malformations and the cortex. Interictal spike discharges were found in the PNH, independent of cortex or mesial temporal structures, in only three patients (4, 5 and 6, Fig. 3). The lack of IEA in nodules of six other patients may be explained by the haphazard organization of the cells within the malformation, and the possibility that neurons generate electrical potentials too small to be recorded with our method (see Discussion). Three distinct SEEG ictal patterns were observed during monitoring.

**SEEG ictal pattern no. 1 (patients 1 and 2)**

Onset was in mesial temporal structures exclusively. These patients had seizure semiology suggestive of temporal lobe epilepsy, and SEEG evaluation showed epileptiform abnormalities confined to the amygdala and hippocampus.
without involvement of the explored heterotopia or evidence of more widespread epileptogenicity. The first patient with bilateral contiguous and diffuse PNH had unilateral hippocampal atrophy, but only one nodule was studied. In this case, this clearly represents a sampling limitation. The second patient also had typical hippocampal atrophy contralateral to a unique nodule of grey matter in the trigone, which was explored. Both had satisfactory surgical outcome after resection of the epileptogenic hippocampus and amygdala (Engel class 3 for patient 1, and class 1d for patient 2) after 8 and 5 years of follow-up. The first patient remained on polytherapy after surgery, while the second is now taking only one antiepileptic drug. The satisfactory result assured us that PNHs did not have a major role in the epileptogenicity of these patients. No heterotopic neurons were found in their pathological specimens, and the hippocampus in both cases showed neuronal loss and gliosis.

**SEEG ictal pattern no. 2 (patients 3 and 4)**

There was focal onset in mesial temporal structures and ipsilateral adjacent heterotopia. One patient (3) presented with clinical features suggestive of mesial and neocortical temporal origin, and the other had a non-specific focal clinical pattern. Both had epileptiform discharges primarily in mesial temporal structures, but with simultaneous involvement of an adjacent heterotopia. The first had a right anterior temporal resection that included the heterotopia abutting the posterior temporal horn but excluded a large parietal subcortical heterotopia, which did not generate independent epileptic activity and was not involved in seizure onset. This patient is seizure free after 1 year follow-up. The second patient had a selective amygdalo-hippocampectomy a year ago with resection of three heterotopic nodules in the wall of the ipsilateral temporal horn and trigone), and so far has been seizure free. Both patients were maintained after surgery on the same drug regimen.
SEEG ictal pattern no. 3 (patients 5, 6, 7 and 8)

A regional or widespread neocortical pattern was found with heterotopia involvement. Patients presented with focal seizures suggestive of temporal or temporo-occipital origin, and surface EEG findings were bilateral or widespread. Two of them had bilateral ectopic grey matter (patients 6 and 8), and another (patient 7), with unilateral temporo-trigonal nodules, had an associated ipsilateral temporo-parietal cortical malformation. The epileptic activity was mostly neocortical, but synchronous or independent epileptic discharges were also recorded from the heterotopia in all cases, as well as from the mesial temporal structures.

In the first patient (5), the epileptogenic area was mainly neocortical, confined to one occipital neocortex, but synchronous with the activity found in the underlying recorded heterotopion (Fig. 4). This patient was the only one of this group to have a very localized lesion and a good surgical outcome (Engel class 1d) after removal of two adjacent occipital heterotopias plus a rim of overlying occipital cortex (5 years follow-up). This patient is now on monotherapy. Histopathological findings showed clusters of large multipolar neurons mixed with smaller neurons and some pyramidal cells in a haphazard fashion. No balloon cell, gliosis or cortical abnormalities were seen in the surgical specimen available for histology.

The second patient (6), the most intractable of the series, had abundant, bilateral and multifocal interictal spikes in the neocortex, amygdala, hippocampus and in the six nodules explored (Fig. 3). Numerous seizures were recorded in this patient, some with focal onset in a nodule (Fig. 5). The majority, however, showed synchronous involvement of the occipito-temporal neocortex, mesial temporal lobe structures and the nodules. A two-step palliative surgical approach was considered, consisting first of a lesionectomy (removal of the nodules through a transcortical and intraventricular approach) and ipsilateral amygdalo-hippocampectomy in the non-dominant hemisphere. She improved somewhat (seizures were reduced by 25–50%) with a follow-up of 1 year. The second surgery will aim at removing only the three nodules lying in the left trigonal area.

In the third patient, almost all seizures originated simultaneously in one heterotopion and overlying temporal neocortex of the non-dominant hemisphere. Rare electrographic seizures were recorded independently from the ipsilateral amygdala. This patient is awaiting surgery and an extensive temporal resection is planned including the amygdala, the temporal horn grey matter nodule and the temporal neocortex, but excluding the hippocampus and the parietal neocortical malformation. Finally, in the fourth patient, epileptic activity was scarce, but independent, in the two PNH explored (one on each side). The main ictal epileptiform activity was in the temporo-occipital cortex just overlying the trigonal heterotopia on both sides. Surgery was not considered in this patient.

In summary, we confirmed that nodules of heterotopic grey matter can generate both normal and abnormal electrical activity. The interictal discharges are independent or synchronous with those from allo- and neocortex. The ictal epileptiform activity recorded from the nodules is usually synchronous with cortical discharges. Three different ictal patterns were found: in the first, the mesial temporal structures are exclusively involved; in the second, we see synchronous

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Fig. 4 Patient 5. Ictal SEEG recording. Regional seizure onset in left occipital lateral neocortex (ln 3–8) and left posterior parahippocampus (li 1–3) with immediate seizure propagation to the anterior hippocampus (lh 1–3).
involvement of mesial temporal structures and adjacent heterotopia; and, in the third, there is a regional or widespread cortical onset with implication of the heterotopia.

**Discussion**

All eight patients had extensive exploration of the epileptogenic area with intracranial depth electrodes, and at least one periventricular heterotopia was studied in each case. This is the first study that attempts to analyse the respective roles of heterotopia, temporal and extra-temporal neocortex and mesial temporal lobe structures in the generation of epileptic activity in a relatively large series of patients with PNH and focal epilepsy. Another aim of the study was to define guidelines and approaches for the evaluation and surgical treatment of patients with intractable focal seizures and PNH.

Invasive electrophysiological evaluations have been reported in very few patients with grey matter heterotopia, and hence analyses that looked at the epileptic activity from both the lesion and surrounding or distant cortex are scarce. The first study came from Morrell et al. (1992) who presented an 11-year-old child with intractable parietal seizures and a band heterotopia (double cortex syndrome) on MRI. Acute peroperative cortical and intra-lesional EEG recording showed that the heterotopic cell population exhibited apparently normal electrical patterns similar to those observed in normally organized cortex, but also high voltage spike-and-wave activity independent of the spikes arising in the adjacent overlying neocortex. No seizures were recorded, but the authors thought that the epileptiform patterns found in the heterotopic tissue exhibited spatial distribution and temporal properties suggesting recurrent inhibition in the heterotopic cortex. Similar findings were found in another patient with band heterotopia who underwent chronic recording with intracranial electrodes (Mai et al., 2003). The authors described, however, synchronous epileptic activity in the band heterotopia and overlying neocortex suggesting anatomical and functional interconnections. In 1994, the Grenoble group (Francione et al., 1994) presented a 29-year-old woman with longstanding focal seizures who had a focal band of heterotopic grey matter in the right temporal white matter (as in our patient 3). Chronic SEEG recording showed low voltage 14–16 Hz fusiform interictal activity independent of or synchronous with temporal interictal activity, independent spikes in the lesion and in the temporo-parietal neocortex, and ictal discharges generated simultaneously, but not independently, in the heterotopia and adjacent temporo-parietal structures. Resection of the lesion and ipsilateral amygdala, hippocampus, temporal lobe and centro-parietal operculum led to seizure freedom at 15 months follow-up. In 1997, we reported a patient with intractable focal epilepsy and a giant subcortical heterotopia (Preul et al., 1997). Abundant epileptiform discharges were recorded from the cortex during acute per-operative electrocorticography, but no spiking from the lesion itself. Normal appearing EEG patterns were recorded from the malformation. In 1998, Kothare and colleagues evaluated three patients with intractable focal seizures and PNH with multiple depth electrodes, including
placement in the PNH, to determine whether seizures originated from the PNH. The heterotopia were focal, left occipital in two patients and bilateral occipital and temporal in the third. They proposed that PNH might serve as an epileptogenic source: in two patients, all seizures arose from the PNH as a low voltage fast β activity with subsequent spread to mesial temporal structures. In the third, 80% arose from the hippocampi with or without simultaneous onset from PNH and 20% from the heterotopia. There was, however, no simultaneous recording from the overlying cortex, and therefore they could not confirm if the seizures started in the PNH or in the overlying neocortex and then spread to the PNH or to mesial temporal structures. None of their patients were operated (Kothare et al., 1998).

From our own data and from the literature, it becomes clear that heterotopia can generate not only normal EEG activity but also interictal and ictal epileptic discharges, usually synchronous with, but sometimes independent from the surrounding allo- or neocortex. Epileptic interictal discharges were found in a nodule in only three of our patients, but all patients had uni- or bilateral mesial temporal spikes (confined to these structures in two), also involving the cortex in the majority, usually overlying the malformations. Heterotopic nodules consist of a large number of cells, some collections in small clusters of 4–5 cells with randomly organized neurons, while others exhibit a pattern suggestive of small clusters of 4–5 cells with randomly organized neurons. Some collections in small clusters of 4–5 cells with randomly organized neurons, while others exhibit a pattern suggestive of small clusters of 4–5 cells with randomly organized neurons. In contrast, some collections in small clusters of 4–5 cells with randomly organized neurons. These studies have suggested that intranodular neurons have altered excitatory or inhibitory transmission. Eksioglu et al. (1996) were the first to demonstrate in an autopsy of a patient with bilateral and diffuse PNH that heterotopic neurons were rich in synaptophysin, a membrane glycoprotein of synaptic vesicles used to investigate synaptogenesis. They could not determine, however, if the synaptic input was from within the nodules or from extranodular structures such as the cortex. Hannan et al. (1999) showed, in surgical specimens obtained from epileptic children with nodular heterotopia, that the heterotopia, either subcortical or subependymal, had sparse connections with each other and with other parts of the hemisphere, including the cortex. They demonstrated that nodules contained immature GABAergic neurons and suggested that the abnormal maturity of the GABA network within nodules may be excitatory rather than inhibitory. They proposed that intrinsic nodular epileptogenicity might be communicated to the cortex, which in turn may act as an amplifier to synchronized excessive activity. Furthermore, they proposed that the local disinhibition secondary to immature GABAergic neurons could also lead to synchronized multisynaptic excitatory interactions and generate prolonged bursts and after-discharges.

There are three experimental rat models that present anatomical and histological similarities with human PNH. The first is the methyloxazymethanol-treated rat model (MAM-rat) where prenatal exposure results in diffuse cortical malformations, including heterotopia especially in the hippocampus (Nagata and Matsumoto, 1969). The second is the telencephalic internal structural heterotopia (tish) rat, a neurological mutant, that exhibits bilateral cortical heterotopia similar to those found in human double cortex (Lee et al., 1997). The third results from exposure of fetal rats to external radiation causing diffuse cortical dysplasia, and subcortical and periventricular heterotopia (Cowan and Geller, 1960).

Different studies using the MAM-rat model described definite connectivity between heterotopia and cortex (Colacitti et al., 1998; Sancini et al., 1998; Smith et al., 1999). The neurons in dysplastic areas in this model are frequently hyperexcitable. Heterotopic neurons in MAM-rats exhibit K+ channel abnormalities resulting in increased neuronal firing (Castro et al., 2001). Alteration of GABAergic circuitry was also demonstrated (Calcagnotto et al., 2002). The authors provided evidence for a significant alteration in inhibitory synaptic function at heterotopic synapses but suggested increased GABA-mediated inhibition that may serve to dampen the intrinsic hyperexcitability in the nodular heterotopia. Other factors were found that can contribute to heterotopic neuron excitability such as limited neuropeptide Y susceptibility (a potent, endogenous modulator of hippocampal excitability) (Pentney et al., 2002), changes in molecular organization of NMDA (N-methyl-D-aspartate) receptor subunits and aberrant connectivity within heterotopia (Castro et al., 2001; Calcagnotto et al., 2002; Pentney et al., 2002; Gardoni et al., 2003). Overall, these changes
could produce an excess of excitatory over inhibitory neuronal circuitry. Interestingly, Baraban and colleagues demonstrated that when the heterotopia are isolated from the hippocampus, they generate seizure-like activity by themselves (Baraban et al., 2000).

Reciprocal connections between normal cortex and heterotopia have also been shown in the tish rat model (Schottler et al., 1998; Chen et al., 2000). Cortical normotopic rather than heterotopic neurons are responsible for initiating epileptiform activity. Connections exist between the heterotopic neurons and the overlying cortex, which contribute to seizure propagation, but the presence of an abnormal adjacent cortex appears in itself important and sufficient to generate seizures. In the third model, a reduction of GABA-mediated inhibitory activity was demonstrated in both the cortex and heterotopic grey matter (Chen and Roper, 2003).

Given the common morphological features seen in human PNH and in rat models, it may be assumed that the same abnormal connectivity exists in humans, explaining the presence of synchronous epileptic discharges in the lesion, the hippocampus and neocortex in our patients (Fig. 6). Their connections with adjacent or distant structures may play a role in amplification and synchronization of epileptiform activity, and may explain the widespread epileptogenic area often described in these patients. Such a network may provide a number of loops, within the PNH and between PNH and overlying cortex, to produce a seizure.

Mesial temporal structures are common epileptogenic substrates (Dalby and Mody, 2001). We demonstrated that mesial temporal structures are also highly epileptogenic in patients with PNH; it appears that the hippocampus is not just an innocent bystander and participates actively in epileptogenesis. The co-existence of hippocampal abnormalities occurs in some patients with cortical developmental disorders, and this could be due to common pathogenic mechanisms during embryogenesis or early development (Raymond et al., 1994; Cendes et al., 1999; Salanova et al., 2004). Six of eight patients had uni- or bilateral hippocampal atrophy and five had uni- or bilateral abnormal shape and positioning of the hippocampus. Considering the two types of abnormalities together, only one patient of our series had normal appearing mesial temporal lobe structures. In our larger surgical series of 20 patients with PNH who had a temporal lobe resection, half had histological or radiological hippocampal atrophy (unpublished data). Although in exceptional cases (e.g. patient 2 of this study), resection of temporal lobe structures in a patient with hippocampal atrophy was sufficient to obtain a good surgical outcome, in the majority this procedure does not result in long-term cessation of seizures (Li et al., 1997).

Finally, abnormalities of cortical architecture, and of cortical neuronal composition and connectivity, may allow the cortex to act as a primary epileptogenic substrate (Preul et al., 1997; Hannan et al., 1999; Sisodiya et al., 1999). Patients with nodular heterotopia have a high incidence of cortical abnormalities such as atrophy and polymicrogyria in addition to hippocampal atrophy (Sisodiya et al., 1995). In our series of 30 patients with subependymal nodular heterotopia, 54% had visually detectable cortical abnormalities (unpublished data). These cortical abnormalities may contribute significantly to

Fig. 6 Patient 6. Interictal SEEG recording. Synchronized epileptic discharges were recorded in the left hemisphere: spike-and-wave 3.5 Hz activity is seen in the amygdala (LA1-2), hippocampus (LH1-2), neocortex (LO3–LO7 and LP5–LP7) and in the three heterotopic nodules (LS1-2, LO1-2 and LP1-2). On the right, less obvious rhythmic activity was recorded involving hippocampus (RH1-2), neocortex (RS7-8 and RC6-7) and at least one nodule (RS5).
the generation of seizures and are often remote from the EEG discharges. This may represent an alternative explanation for the failure of temporal resections.

In summary, patients with PNH and epilepsy represent a heterogeneous group. Seizures result from complex interactions between PNH and allo- or neocortex. Because of the variety of demonstrated mechanisms and patterns of epileptogenesis, invasive recordings are essential in patients considered for surgical treatment. In some instances, it seems that the PNH needs to be removed to stop the epileptogenic process. At other times, the heterotopia appear to have an indolent role and may not be involved in the epileptic network. The results of our electrophysiological studies, however, provide a definite role for the hippocampus and neocortex in the generation and propagation of seizures. When only few neighbouring unilateral PNH are present, investigation by SfEEG may indicate a focal resection, with or without inclusion of the PNH, and a good outcome may be expected. Bilateral multiple or contiguous PNH are often associated with widespread epileptogenesis, where classical surgical approaches are unlikely to be effective. Stereotactic or endoluminal ablation of the heterotopia with or without resection of the hippocampus and neocortical structures may be considered. Experimental work using animal models and human tissue from surgical resections, and analysis of the epileptogenic area with functional methods such as diffusion studies, EEG–functional MRI and magnetic resonance spectroscopy, should help clarify the relationship existing between the heterotopia and allo- and neocortex.

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References


