Case Report

Successful Treatment of Epilepsy by Resection of Periventricular Nodular Heterotopia

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We report on a case of successful surgical treatment of drug-resistant epilepsy associated with a solitary lesion of periventricular nodular heterotopia (PNH). In the reported patient, intracranial ictal electroencephalography disclosed that seizures did not originate from the heterotopic nodules. However, the seizures were completely suppressed by lesionectomy of PNH alone. Epileptogenesis associated with PNH likely involves a very complex network between PNH and the surrounding cortex, and the disruption of this network may be an effective means of curing intractable, PNH-associated epilepsy.

Key words: periventricular nodular heterotopia, epilepsy, surgery, ictal electroencephalography

P eriventricular nodular heterotopia (PNH) is a type of brain malformation characterized by persistence of cells in the ventricular zone during cortical development. PNH consists of round nodular masses of normal-appearing neurons and glial cells with no laminar organization, located close to the periventricular germinal matrix [1]. Patients with PNH often have intractable epilepsy that has clinical features suggestive of temporal lobe epilepsy but that cannot be cured by temporal lobectomy [2].

The process of seizure generation in epilepsy associated with PNH is very complex, and it is thought to involve the heterotopic lesion as well as the overlying cortex. The localization of the epileptogenic zone by intracranial electroencephalography (EEG)

prior to resective surgery is not easy in this disorder [3, 4]. We report on a patient who, prior to surgery, suffered from long-lasting drug-resistant epilepsy associated with PNH. The successful outcome in this case may provide insight into the mechanisms of epileptogenesis linked to PNH.

Case Report

The male patient was 35 years of age at the time of surgery. He had no remarkable family history.

His development was uneventful before the onset of epilepsy at 13 years of age, when the initial generalized convulsive seizure occurred. Antiepileptic treatment consisting of sodium valproate was begun at a local hospital, but convulsive seizures continued to occur several times per year. Complex partial seizures (CPSs) with motion arrest and oral automatism also occurred from 16 years of age. The frequency of

seizures, most of which were CPSs, increased from 25 years of age: weekly seizures persisted in spite of medical treatment using a number of antiepileptic drugs (AEDs), including phenytoin and carbamazepine.

During an admission to the National Epilepsy Center at Shizuoka, MRI disclosed a solitary lesion of PNH in the paratrigonal white matter region of the right lateral ventricle (Fig. 1A–C). This lesion was isointense to gray matter and included a cyst-like low-intensity region. Interictal scalp EEGs showed bilateral temporal dominant low-amplitude spikes and polyspikes. Ictal scalp EEGs of CPSs showed bilateral, particularly right, temporal dominant rhythmic fast discharges that gradually slowed down in association with disturbance of consciousness (Fig. 2). Other noninvasive evaluations of the epileptogenic region

were made: magnetoencephalography (MEG) indicated that the estimated dipole sources of interictal epileptic discharges were loosely clustered in the right temporal lobe (Fig. 3AB). ^{99m}Tc-ethylcysteinate dimer (ECD) single-photon emission computed tomography (SPECT) did not reveal any abnormality of perfusion during the interictal period (Fig. 3C), but it disclosed areas of ictal hyperperfusion including the vicinity of PNH, as depicted in a subtraction ictal SPECT coregistered to MRI (SISCOM) image (Fig. 3D). The results of ^{123}I iomazenil SPECT were not remarkable.

We performed invasive EEG monitoring to localize the seizure onset zone by implanting three bundles of depth electrodes stereotactically targeting the lesion of PNH using an image-guided system (Medtronic Inc., Minneapolis, MN, USA). We also placed subdural
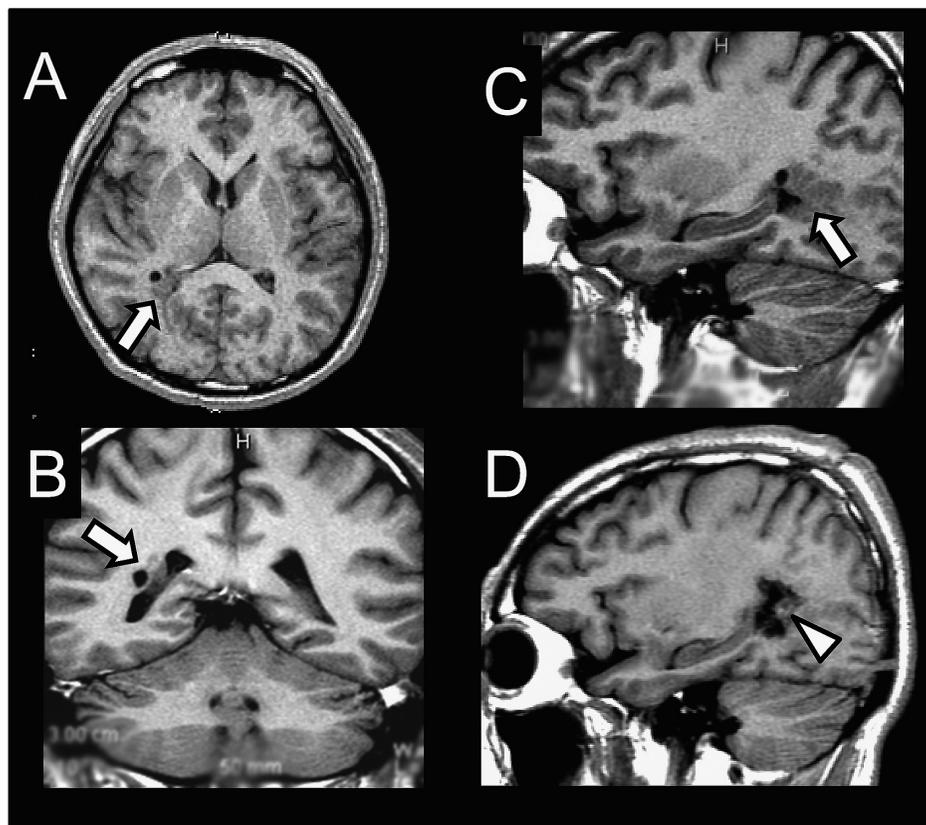

Fig. 1   MRI. T1-weighted image showing a solitary lesion of periventricular nodular heterotopia (PNH) in the paratrigonal white matter region of the right lateral ventricle; the lesion is isointense to gray matter and includes a cyst-like low-intensity region (A axial, B coronal, C sagittal; arrows). The postoperative T1-weighted sagittal image shows a small cavity after lesionectomy (D).
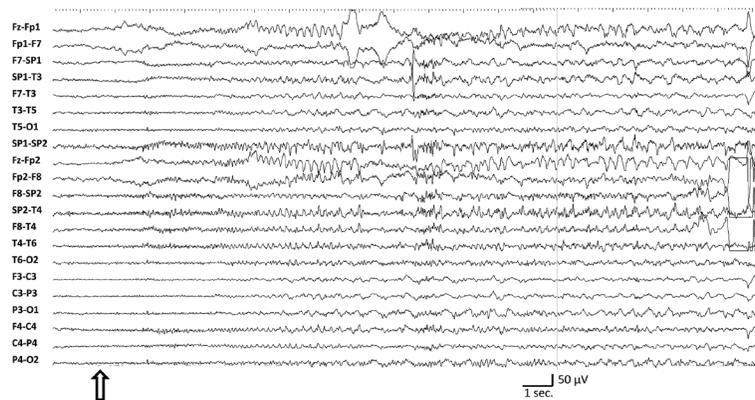
Fig. 2   Scalp ictal EEG of a complex partial seizure. The patient showed brief motionless staring without aura from around the time-point indicated by the arrow. In the concomitant EEG, rhythmic fast discharges appeared with bilateral, particularly right, temporal dominance and gradually slowed down. We used sphenoidal electrodes (SP1, left; SP2, right) in addition to the international 10–20 electrode placement system.

electrodes to cover wide cortical areas of the parietal, occipital and temporal lobes (Fig. 4). Interictal intracranial EEGs showed numerous polyspikes in the right superior temporal gyrus but not in the heterotopic nodules. Ictal intracranial EEGs captured four seizures with secondary generalization during a 14-day recording session, and revealed initial fast activity in the right superior temporal gyrus and the mesial surface of the right occipital lobe at the time of clinical seizure onset and subsequent widespread involvement (Fig. 5). The involvement of the PNH lesion in seizure discharges was only secondary. Because such simultaneous seizure onset from 2 separate cortical regions is unlikely, it was suggested that the true seizure onset zone was missed and that all of the recorded seizure discharges were secondary phenomena.

Therefore we only performed a lesionectomy of the PNH because no other brain regions were considered resectable (Fig. 1D). Fortunately, however, the patient has remained seizure-free for 5 years and 4 months following the surgery. The surgical procedure consisted of an approach from the bottom of the posterior end of the Sylvian fissure. Histology of the resected specimen confirmed heterotopia. The patient had no neurological deficits after the surgery. Follow-up scalp EEGs showed only sporadic right temporal sharp waves.

Discussion

The present patient has attained freedom from seizure following a lesionectomy of PNH, even though invasive EEG monitoring indicated that his seizure onset zone was not in the heterotopic nodules. This case illustrates the complexity of epileptogenesis associated with PNH.

In previous studies on seizure origin in epilepsy associated with PNH, some authors have reported that seizure generation occurs within PNH lesions [5, 6], while others have reported that it occurs outside of PNH lesions [7]. Tassi et al. investigated 8 patients using electrodes contacting heterotopic nodules and the overlying cortex, and found simultaneous activation of a nodule and the cortex in 5 cases and seizure origination from the cortex in the remaining three [4]. In the report of Aghakhani et al. on 8 patients, the ictal activity involved the nodules synchronously with the overlying cortex or ipsilateral hippocampus in 6 patients, and involved only the mesial temporal structures in the other 2 [3]. Thus PNH, a malformation resulting from improper cortical development, is likely associated with abnormalities of the surrounding cortex.

Likewise, seizure generation in PNH has been suggested to stem from an epileptogenic network involving not only PNH but also the neighboring cor-
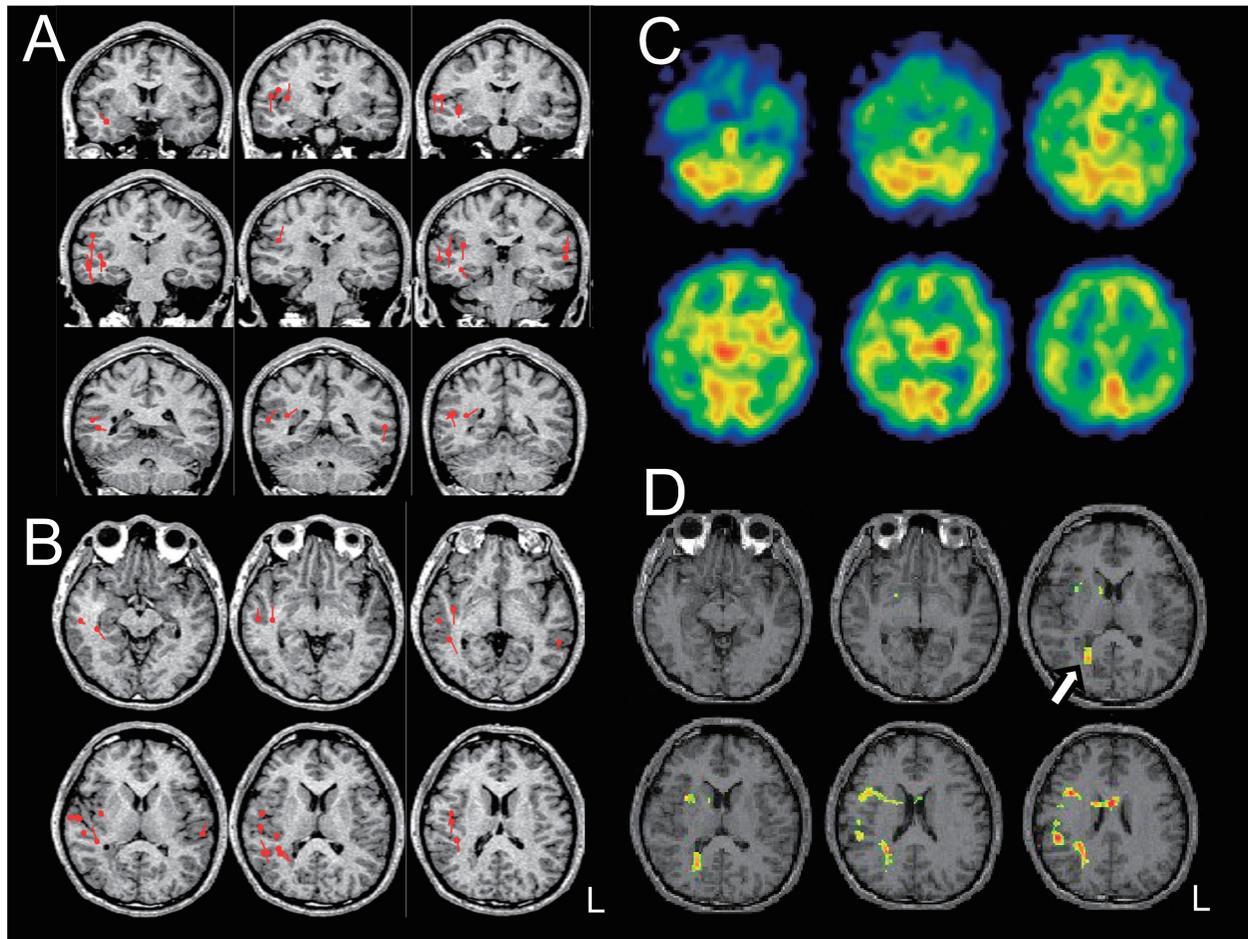
Fig. 3   Noninvasive evaluations of the epileptogenic region. Magnetoencephalography (MEG) indicated that the estimated dipole sources of interictal epileptic discharges were loosely clustered in the right temporal lobe, as depicted on MRI (**A** coronal, **B** axial). Single-photon emission computed tomography (SPECT) did not reveal any abnormality of perfusion during the interictal period (**C**), but it disclosed areas of ictal hyperperfusion in the right fronto-temporo-parietal lobe including the vicinity of PNH, as depicted in a subtraction ictal SPECT coregistered to MRI (SISCOM) image (**D**, arrow).

tex [3]. Although some patients are relieved only by cortical resection [3], there has been a report of successful radiofrequency lesioning of PNH as well [8]. The mechanisms of epileptogenesis associated with PNH must therefore be very complex, and it may be critical to disrupt the epileptogenic network through surgery. In the current patient, it was revealed that the epileptogenic network involved a large area of the brain, based on the results of inter-ictal and ictal EEG, MEG, and SPECT. In this case, the surgery may have been successful because the lesionectomy effectively disrupted the epileptogenic

network, in spite of the fact that PNH alone was resected and that PNH itself was apparently not directly involved in ictogenesis.

Most PNH cases can be classified into one of several well-defined subgroups, including a heterogeneous group [9], but the type of PNH in the current patient does not belong to any of these, to our knowledge. There is a type of bilateral and symmetrical PNH that is observed mostly in female subjects. Specifically, defects in the filamin A gene (*FLNA*) result in an X-linked form of bilateral PNH [10], which is seen almost exclusively in female patients and

which accounts for 100% of familial cases and 26% of isolated female cases [11]. Mutations in the *ARFGEF2* gene have been identified as responsible for an autosomal recessive form of bilateral nodular heterotopia in 2 consanguineous families with microcephaly, severe developmental delay, and early-onset
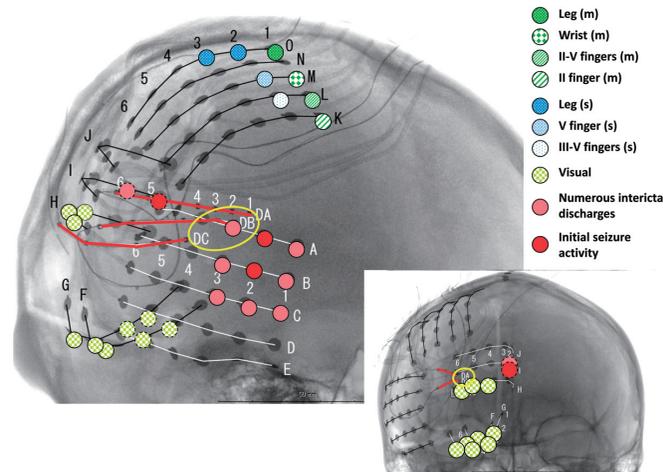

Fig. 4   Intracranial electrodes. Depth electrodes (DA, DB, DC) and subdural electrodes (A–O) are shown on a skull X–ray image (top-left: sagittal view; bottom-right: coronal view). The bundles of depth electrodes are depicted by red lines, and the approximate location of PNH is indicated by the yellow ellipses. The results of functional cortical mapping are indicated with respect to motor responses (m: left leg, wrist, II–V fingers, II finger), sensory responses (s: left leg, V finger, III–V fingers), and visual responses. The electrodes recording numerous interictal epileptic discharges (pink) and the initial seizure activity (red) are also shown. The placement of these electrodes corresponds to that of the electrodes used to collect the data (Fig. 5).
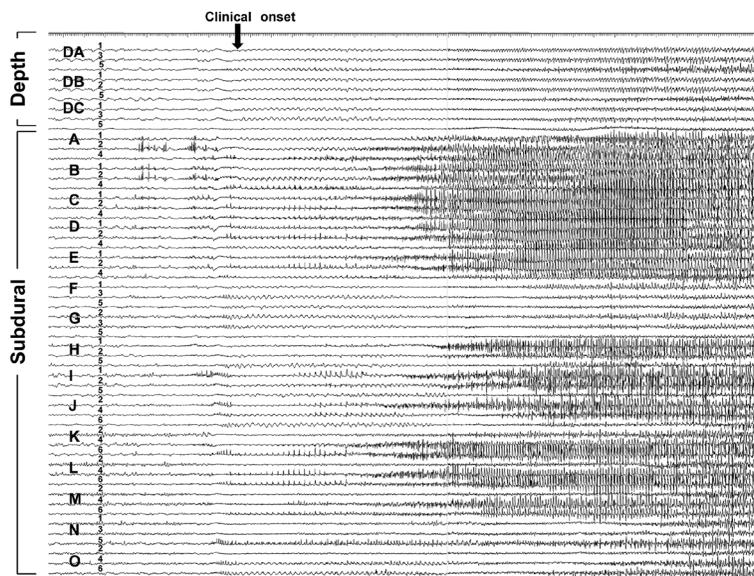

Fig. 5   Ictal intracranial EEG (placement of the electrodes indicated in Fig. 4). The initial rhythmic fast activity was recorded from the right superior temporal gyrus (A2, B2) and the mesial surface of the right occipital lobe (I1) at the time of clinical seizure onset. The ictal discharges subsequently spread to secondarily involve various cortical regions and the PNH.

seizures [12]. The current male patient had a solitary lesion of PNH with no remarkable family history, so his clinical findings are quite different from those of the genetic disorders.

The process of epileptogenesis may vary among cases of PNH. Surgical treatment of PNH is a challenge, but it is worth the effort to overcome its associated medically uncontrollable epilepsy. As our experience with the current patient indicates, when the seizure origin cannot be precisely identified even by invasive EEG monitoring, a lesionectomy of PNH alone, which is less invasive compared with cortical resection or temporal lobectomy, may be beneficial as it may disrupt an epileptogenic network.

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