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Case report

A case report of surgically treated drug resistant epilepsy associated with subependymal nodular heterotopia

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ABSTRACT

Subependymal nodular heterotopia (SNH) is a cortical development malformation that is commonly associated with medically resistant epilepsy. Cases of SNH are challenging to treat surgically because there are typically multiple nodules, which may be involved in epileptogenesis. Moreover, dual pathology may exist in these patients. Here, we present a case with unilateral subependymal heterotopic nodules associated with ipsilateral hippocampal atrophy. Invasive and non-invasive work-ups revealed that the hippocampus was the actual ictal onset zone and that the SNH was not involved. An anterior temporal lobectomy was carried out, and postoperative seizure outcome was class Ia at the end of 2 years. The case demonstrates that SNH may not play a major role in patients with dual pathology. However, direct electroencephalography (EEG) recording from areas of SNH and other possible epileptogenic regions is indispensable in defining the ictal onset zone and avoiding poor surgical outcomes.

1. Introduction

Subependymal nodular heterotopia (SNH) is a cortical development malformation that is close to the periventricular germinal matrix and made up of round, nodular masses of normal neuroglia that lack laminar organisation.[2,5,6,15] Regardless of whether SNH are bilateral, symmetric or unilateral, the main clinical issue is medically refractory focal epilepsy. It is proposed that epilepsy in SNH patients is the result of complex interactions between heterotopic nodules and adjacent archicortical and neocortical areas. Although there are conflicting results in terms of surgical outcome, epilepsy surgery can be favourable after a careful assessment of seizure-generating structures and after establishing a rationale for surgical approach.[12,14,18,19] Here, we present a surgically treated patient with drug resistant focal epilepsy whose MRI was consistent with unilateral SNH and ipsilateral hippocampal atrophy.

2. Case description

A twenty-seven-year-old woman with a history of intractable epilepsy was admitted for pre-surgical evaluation. Her seizures started when she was 10 months old and occurred 2–3 times a month, lasting less than 2 min. Her parents described her daytime seizures as "a staring event where she does not respond but gulps repeatedly and picks at her clothes". Phenytoin and carbamazepine partially controlled her seizures until she was 9 years old. Following a secondarily generalised tonic–clonic seizure at the age of 12 years she was put on valproic acid, but different antiepileptic drug combinations did not effectively control the seizures. At the time of admission she had 1–2 seizures per week, despite a combination of valproic acid, lamotrigine and levetiracetam. She did not have a history of prenatal problems but was delivered by forceps. Early developmental milestones were not delayed. She had a prolonged febrile convulsion (more than 15 min) at 16 months. She was able to complete 8 years of compulsory education but could not attend high school because of frequent seizures. She was unemployed and did not have a driving licence. Her family history was unremarkable for epilepsy.

The scalp video-EEG demonstrated interictal right frontotemporal epileptiform discharges. She could clearly define her auras, which were primarily feelings of déjà vu and sometimes fear. In video-EEG monitoring unit 3 habitual seizures were recorded, and they began with staring, loss of responsiveness and swallowing, followed by incoherent speech, which progressed to dystonic posturing of the left arm and a postictal confusion period. Her seizures generally lasted 8–10 min. The ictal video-EEG documented rhythmic delta activity in the right anterior temporal electrodes prior to the clinical seizure. The cranial MRI showed

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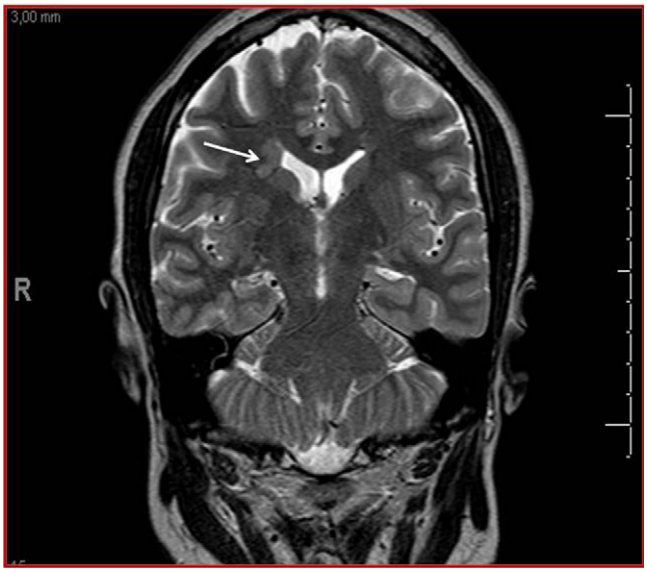


Fig. 1. T2-weighted coronal sections showing multiple nodules consisting of grey matter along the paratrigonal region of the right lateral ventricle (arrow). The ipsilateral side shows volume loss in the hippocampus and parahippocampal gyrus and a significant signal change.

unilateral periventricular multiple nodules that consisted of grey matter located along the paratrigonal region of the right lateral ventricle without an extension to the overlying cortex. Additionally, hippocampal atrophy with loss of digitations and T2 signal change ipsilateral to the SNH was evident (Fig. 1). She had no agenesis or hypogenesis of the corpus callosum, malformations in the cerebellum, basal ganglia or thalamus and no extension to the overlying cortex.

Magnetic resonance spectroscopy showed reduced N-acetyl-aspartate (NAA) concentration and NAA/creatine in the right hippocampus. The fluorine-18 (F-18) fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed decreased uptake in the right temporal region compared to the left. Neuropsychological testing (NPT) revealed moderate attention and verbal memory recall deficits, which were consistent with her mildly reduced IQ and mild deficit in abstracting capacity. The Bender–Gestalt test assessing visuomotor and visuospatial abilities was normal. Surgical planning was performed on the basis of the pre-surgical non-invasive work-up designating the right temporal lobe as the possible ictal onset zone. However, it was not possible to estimate the extent of heterotopic nodules that contributed to the onset of seizures. Therefore, in the multidisciplinary pre-surgical conference, we decided to perform an invasive work-up. A subdural grid covering the right temporal neocortex was implanted via standard craniotomy under general anaesthesia, and two depth electrodes were stereotactically implanted in the hippocampus and the SNH. Invasive ictal recordings revealed that habitual seizures started from the right hippocampus, and the heterotopic nodules were silent throughout the ictal period (Figs. 2 and 3). Furthermore, electrocortical stimulation of the hippocampus via depth electrodes evoked a typical aura of déjà vu. A standard anterior temporal lobectomy with amygdalohippocampectomy was carried out, and the nodules were spared. Neuropathological examination of the surgical specimen revealed characteristic patterns of neuronal loss in the CA1 region of the hippocampus.

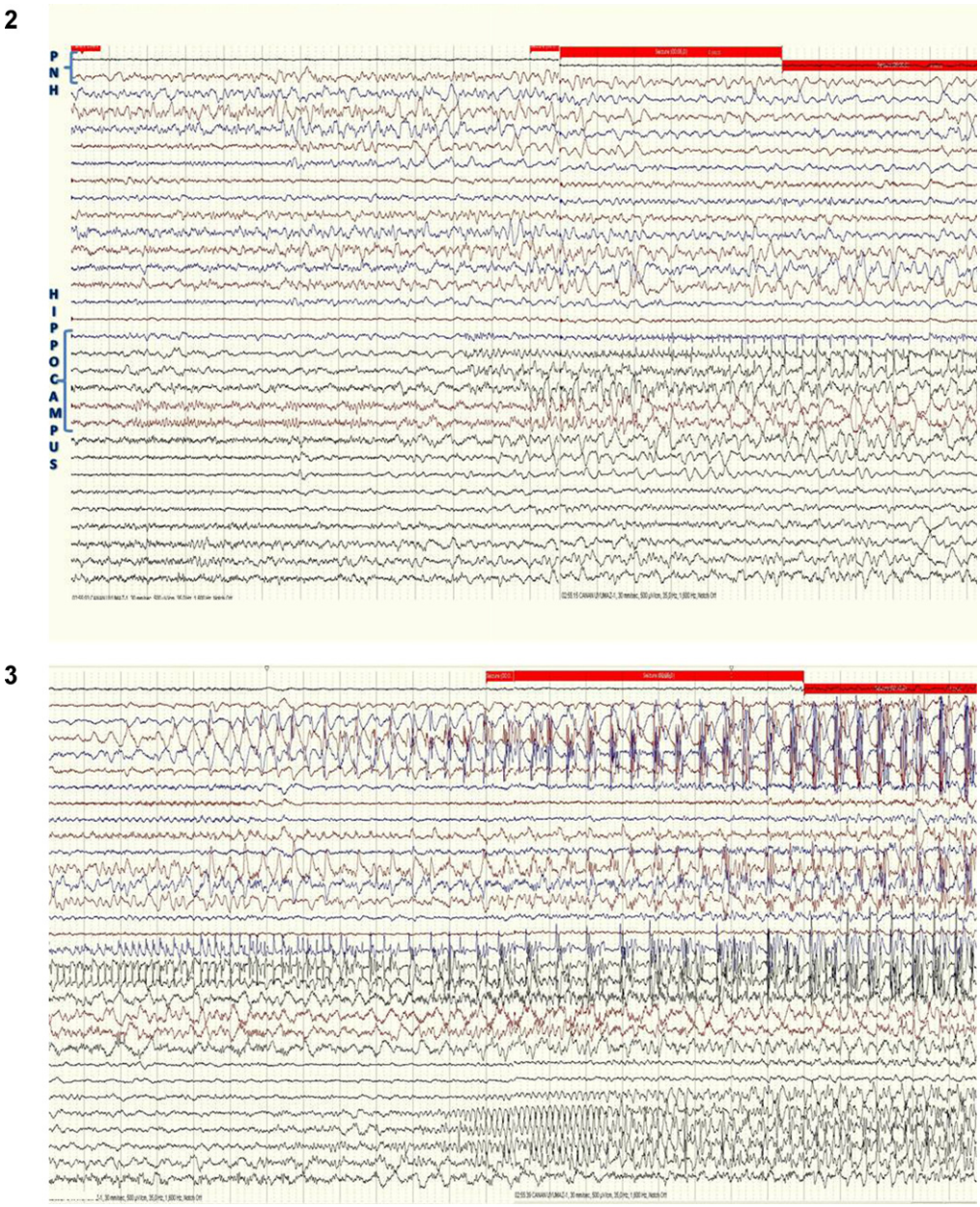
In the early postoperative period, she was on combination therapy of valproic acid (1250 mg), lamotrigine (200 mg) and levetiracetam (1000 mg) daily. Post-operative seizure outcome was excellent at the end of the first year and allowed her to quit valproic acid and reduce the lamotrigine dosage. At her last follow-up visit, she was on 1000 mg of levetiracetam and 100 mg of lamotrigine daily and had been seizure-free for 2 years. Post-operative NPT revealed that her mild memory deficits were unchanged.

3. Discussion

Subependymal heterotopia is a neuronal migration disorder characterised by nodules of neuron clusters due to migration arrest or failure of neuroblasts to undergo apoptosis.[4,9] The nodules may appear in the subpial, subcortical or subependymal regions. The subependymal nodules are the most common form of grey matter heterotopias, which are located close together and form irregular lumps adjacent to the lateral ventricles, bilaterally or unilaterally.[13] Radial glial fibres act as guides for migrating neurons; direct damage to these fibres and deficiency of adhesion molecules essential for migrating neuroblasts may lead to mislocalised neuronal clustering. Neuroimaging with high-resolution MRI can clearly delineate subependymal heterotopias most frequently located in the paratrigonal region and frontal horns of the lateral ventricles.[3,21]

Independent of being uni- or bilateral, the main problem associated with SNH is epilepsy, which can present as both partial and generalised seizures. Moreover, SNH can also be observed in patients without epilepsy; therefore, it is not clear whether heterotopic nodules are the direct cause of epilepsy or a marker of a more widespread abnormality.[13,16,21] SNH can also be a component of dual pathology. Hippocampal sclerosis is associated with various types of cortical dysgenesis, most commonly with nodular heterotopia.[13] In a series of 10 patients, two patients had unilateral hippocampal abnormalities and ipsilateral SNH.[13] Tassi et al.[19] reported that one of those patients was seizure-free following a temporal corticectomy with partial hippocampectomy. However, the hippocampal tissue did not show typical signs of hippocampal sclerosis but did have reactive gliosis.[19] Raymond et al.[13] reported that two patients with concomitant hippocampal sclerosis achieved seizure freedom or improved seizure control after standard anterior temporal lobectomies. Dubeau et al.[7] reported on a series of 33 patients with SNH; 2 of the seven patients undergoing anterior temporal lobectomy achieved seizure freedom, but the others did not improve at all. A report by Li et al.[12] with 10 patients showed that one of them was similar to our case with unilateral SNH and hippocampal sclerosis and was class II post-operatively. These studies have suggested that heterotopic nodules may have variable epileptogenicity. Unfortunately, it is not possible to make absolute conclusions because some of the cases were not studied with invasive monitoring to determine seizure origin. However, several studies utilising invasive monitoring of heterotopic nodules revealed that most of them experience epileptic activity of their own accord at seizure onset, which is synchronous with the overlying neocortex or ipsilateral hippocampus.[1,11,19] Moreover, interictal recordings also showed that these neuron clusters are capable of generating their own epileptic activity.[1,11,19] Although these studies demonstrate connectivity between nodules, overlying cortex and distant cortical structures, the role of heterotopia in seizure generation is not clear. Functional imaging studies during EEG monitoring showed that seizures were generated by the overlying cortex but not the heterotopia.[10,20] Nevertheless, the connections between nodules and other cortical structures may be involved in amplification and synchronisation of epileptic activity, and these roles may explain the widespread epileptogenic networks in these patients.

In our case, an aura suggesting mesolimbic temporal origin and unilateral interictal temporal epileptic abnormalities with findings of unilateral SNH led to further investigations. A PET scan and MR spectroscopy revealed an ipsilateral hippocampal abnormality



Figs. 2 and 3. The first two channels were recorded from depth electrodes implanted in the SNH and the 5 middle channels represent depth electrodes in the right hippocampus. Other channels were recorded from grid electrodes on the anterior temporal neocortex. The patient was asked to press a button at seizure onset, and 2–3 s later rhythmic, fast activity appeared that evolved to spike discharges The SNH were silent throughout the ictal period. Epileptic discharges spread to temporal neocortical areas.

with the heterotopic nodules. We also performed invasive monitoring that verified the non-invasive work-up and clinical features and designated the right hippocampus as the epileptogenic zone. Furthermore, electrocortical stimulation of the hippocampus led to a habitual aura whereas PNH stimulation did not cause any clinical sign or symptom. Our surgical strategy was based on the congruence of the invasive and non-invasive evaluations, and the patient's post-operative outcome indicated that a crucial region of the epileptogenic zone was removed. Moreover, in the long-term follow-up, she will probably experience a recurrence of seizures. For refractory mesial temporal lobe epilepsy with hippocampal sclerosis, there is a high risk of seizure recurrence after surgery, irrespective of pathology.[8,17] Refractory epilepsy is a widespread pathology whether the underlying cause is hippocampal sclerosis or cortical development malformations; therefore, it is difficult to say that we can totally cure refractory epilepsy through surgery. We do not know whether our patient has a cortical abnormality in the overlying cortex or whether there are other connections with distant cortical structures that may lead to seizure recurrence. So far, it is obvious that the outcome is favourable, as a result of either removal of the pacemaker or disconnection.

In conclusion, in cases with unilateral SNH, the best predictor of the surgical outcome is the determination of the ictal onset zone. Therefore, invasive monitoring of possible epileptogenic zones provides the best scientific analysis of the ictus and is the gold standard in planning surgical strategies. However, SNH may not necessarily play a major role in the epileptogenicity of patients with dual pathology. Therefore, because of the variability of the heterotopic nodule epileptogenicity, direct recording of SNH in addition to other possible cortical areas is indispensable in defining the ictal onset zone and avoiding poor surgical outcomes.

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