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Letter to the Editor

Single Pulse Electrical Stimulation Identifies Epileptogenicity in a Case With Subcortical Nodular Heterotopia and MRI Negative Epilepsy

Approximately 30% of people with epilepsy do not achieve remission with medical therapy and are candidates for surgical management [1]. Key investigations in such patients include magnetic resonance imaging (MRI) and scalp electroencephalography [2]. These investigations may yield contradictory results and further investigations with intracranial electrodes may be required.

At our centre, single pulse electrical stimulation (SPES) is performed as part of the standard intracranial evaluation. Two main types of responses to SPES have been described: early and delayed responses to SPES. Early responses occurred immediately after the stimulus and appear to be normal cortical responses to SPES. Delayed responses resemble epileptiform discharges [3] occurring with latencies longer than 100 ms after some stimuli. Essentially, areas showing delayed responses tend to coincide with regions involved at seizure onset in adults [4] and children [5], and their removal is associated with good seizure outcome [4]. Consequently, abnormal responses to SPES can be regarded as an interictal marker for the seizure onset zone [6].

We present a patient with normal MRI and intractable epilepsy. Spontaneous seizures during intracranial telemetry revealed a regional seizure onset over the lateral and anterior aspect of the left frontal lobe, but SPES unexpectedly showed delayed responses apparently arising in an area of white matter. Surgical resection was performed and histopathological examination demonstrated previously unsuspected subcortical nodular heterotopia.

A 30-year-old right handed male presented with a history of seizures from the age of four years when he had a blank episode with aphasia lasting for two hours. At the age of two years he fell from a chair and lost consciousness. At age 12, he suffered a nocturnal generalized tonic-clonic seizure. At the time of evaluation he presented with: a) Simple partial seizures lasting for 5–10 s, with speech loss and tingling/paresis in the right hand (1–2 per day); and b) Complex partial seizures with eye version to the right, left hand automatisms and dystonic posturing of the right hand (6 per day). Drug treatments trialed included 12 different drugs without adequate seizure control.

MRI epilepsy protocol (1.5T) and computed tomography (CT) showed no abnormality. Interictal scalp EEGs showed left frontocentral abnormalities and bifrontal polyspike discharges. Ictal scalp recordings showed bifrontal EEG seizure onset with generalized sharp and slow activity.

A hypothesis of a left frontal seizure onset was tested by stereotactic implantation under MRI guidance of one 8-electrode subdural strip and five depth electrode bundles implanted bilaterally over frontal structures (AdTech Medical Instruments Corp., WI, USA). Each depth electrode bundle consisted of 7–10 cylindrical 2.3 mm long platinum electrodes separated by 5 mm (Fig. 1A and B).

Onset of spontaneous seizures suggested that the seizures had a regional onset over the lateral and anterior aspect of the left frontal lobe (see Fig. 1E).

SPES was carried out through all pairs of adjacent electrodes with pulses of 1 ms duration and 6 mA intensity at a frequency of 0.2 Hz. Delayed responses to SPES were seen at the anterior aspect of the left frontal lobe, involving electrodes mainly located within white matter (Fig. 1C), suggesting that this region was hyperexcitable and potentially epileptogenic. SPES through the electrodes that recorded delayed responses provoked seizures similar to patient's habitual attacks (Fig. 1D). No clear delayed or repetitive responses were seen at other locations despite the presence of early responses to SPES. The areas identified as epileptogenic by SPES were more localized than those involved in spontaneous seizure onset.

The patient underwent resection of the cortex and white matter surrounding the electrodes that induced delayed responses and showed seizure onset, including the pole and anterior third of the left frontal lobe (Fig. 1H). On histopathological examination of the resected specimen, multiple small well-demarcated nodules of heterotopic gray matter were present in the subcortical white matter, the largest measuring 0.4 cm in maximum diameter. The larger nodules (Fig. 1F), consisted of slightly lobulated aggregates of mature neurons surrounded by neuropil which included glial cells and haphazardly orientated myelinated axons (Fig. 1G). In addition, there were tiny groups of neurons in the white matter adjacent to the nodules and elsewhere there was a diffuse increase in white matter neurons (Fig. 1G). Normal laminar architecture was preserved in the overlying cortex.

Five years following surgery he has had a >90% improvement in seizure control with approximately one seizure per week, compared with up to eight seizures per day prior to surgery (Engel outcome grade III).

Discussion

Malformations of cortical development such as nodular heterotopia account for up to 18% of cases of intractable epilepsy [7], and up to 26% of surgically treated cases of pediatric epilepsy [8]. Although the association between nodular heterotopias and seizures is well established, it is not clear if all seizures originate from heterotopic lesions, nor if all nodules are epileptogenic [9,10].

Delayed responses to SPES are related to seizure onset zone and histopathological abnormalities, and consequently are an indirect marker for epileptogenicity [8]. In the present case, SPES induced delayed responses in white matter and also a clinical seizure, providing direct *in vivo* evidence that subcortical nodular heterotopia in man can be epileptogenic. In addition, this demonstrates the

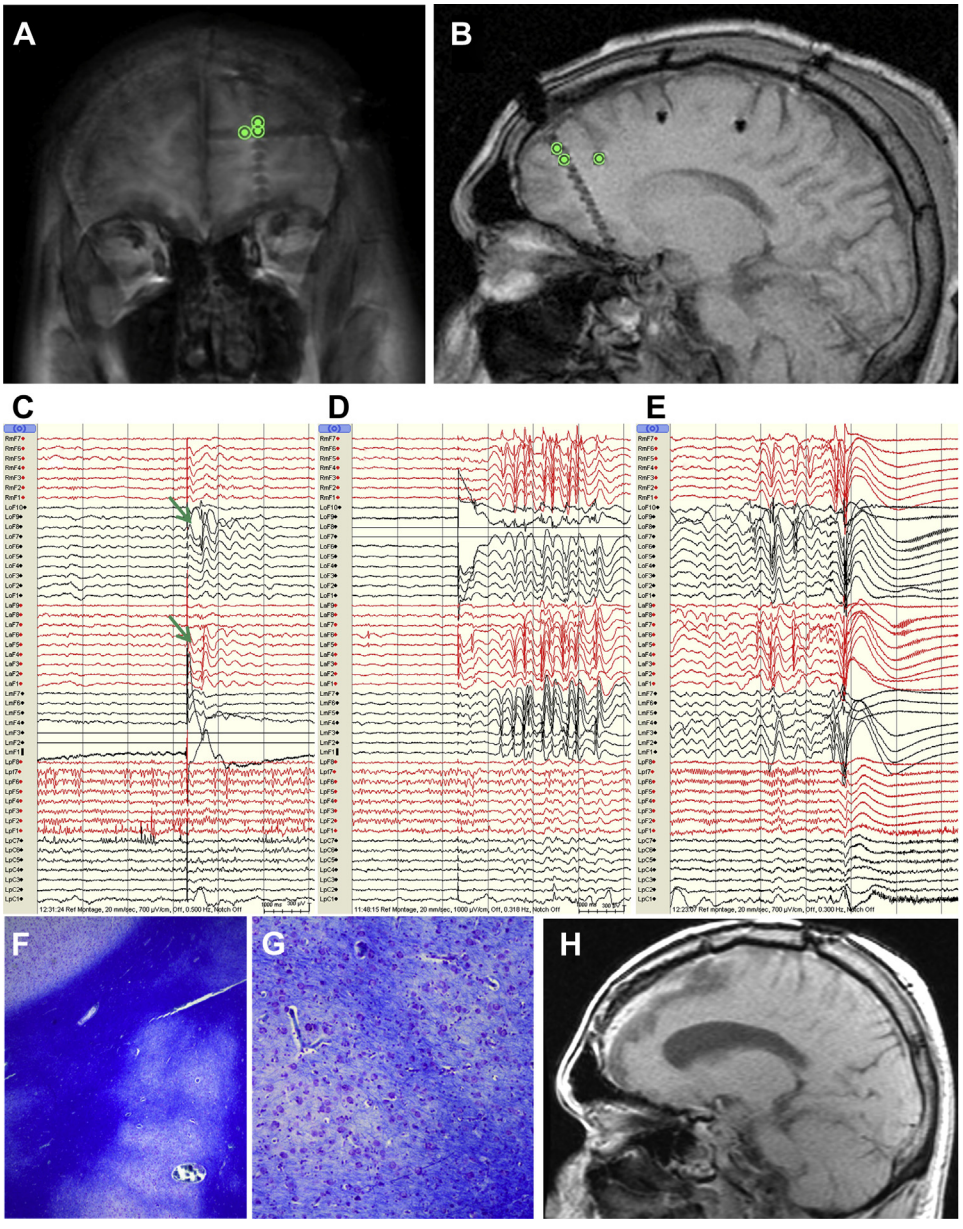

Figure 1. A) Thick slice coronal MRI showing location of depth electrode bundles that generated abnormal single pulse electrical stimulation (SPES) responses (green dots); B) Sagittal view showing location of electrodes; C) SPES through electrodes LmF 2 and 3. Delayed responses generated at electrodes located at the white matter area (green arrows); D) Clinical seizure generated by SPES when stimulating electrodes 8 and 7 of the LoF bundle; E) Intracranial recording of a patient's typical spontaneous seizure; F) Circumscribed island of heterotopic gray matter in subcortical white matter. Darkly stained myelinated nerve fibers within the nodule give it a lobulated appearance. Luxol fast blue/Nissl; G) aggregates of mature neurons with scattered glial cells surrounded by neuropil and myelinated nerve fibers. Luxol fast blue/Nissl; H) Sagittal MRI showing resection cavity. RmF = Right mid frontal; LaF = Left anterior frontal; LoF = Left orbitofrontal; LmF = Left mid frontal; LpF = Left posterior frontal; LpC = Left pre Central. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

utility of SPES carried out through depth electrodes in identifying abnormal white matter regions that appeared normal on MRI at 1.5T.

Seizure control improved significantly after surgery supporting the hypothesis that epileptogenic tissue was removed. However, the patient did not become seizure free. Although SPES identified a non-suspected pathological region, subcortical nodular heterotopia is commonly multifocal and widespread and it is likely that abnormal tissue was left behind, as is often the case in frontal resections.

Our findings support the concept that subcortical heterotopic nodules can be epileptogenic in nature. Furthermore, in this patient with normal MRI, SPES could identify subcortical heterotopic nodules. SPES represents a useful tool in the neurophysiologist's diagnostic kit in identifying the location of epileptogenesis in cortical and subcortical structures. We advocate the use of SPES as an additional tool in the invasive investigation of epilepsy.

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