

# TO SLEEP, PERCHANCE TO SEIZE: SURGERY AMELIORATES NOCTURNAL FRONTAL LOBE SEIZURES

**Surgical Treatment of Drug-resistant Nocturnal Frontal Lobe Epilepsy.** Nobili L, Francione S, Mai R, Cardinale F, Castana L, Tassi L, Sartori I, Didato G, Citterio A, Colombo N, Galli C, Lo Russo G, Cossu M. *Brain* 2007;130 (Pt 2):561–573. Of the cases with nocturnal frontal lobe epilepsy (NFLE) 30% are refractory to antiepileptic medication, with several patients suffering from the effects of both ongoing seizures and disrupted sleep. From a consecutive series of 522 patients operated on for drug-resistant focal epilepsy, 21 cases (4%), whose frontal lobe seizures occurred almost exclusively (>90%) during sleep, were selected. All patients underwent a comprehensive pre-surgical evaluation, which included history, interictal EEG, scalp video-EEG monitoring, high-resolution MRI and, when indicated, invasive recording by stereo-EEG (SEEG). There were 11 males and 10 females, whose mean age at seizure onset was 6.2 years, mean age at surgery was 24.7 years and seizure frequency ranged from <20/month to >300/month. Nine patients reported excessive daytime sleepiness (EDS). Prevalent ictal clinical signs were represented by asymmetric posturing (6 cases), hyperkinetic automatisms (10 cases), combined tonic posturing and hyperkinetic automatisms (4 cases) and mimetic automatisms (1 case). All patients reported some kind of subjective manifestations. Interictal and ictal EEG provided lateralizing or localizing information in most patients. MRI was unrevealing in 10 cases and it showed a focal anatomical abnormality in one frontal lobe in 11 cases. Eighteen patients underwent a SEEG evaluation to better define the epileptogenic zone (EZ). All patients received a microsurgical resection in one frontal lobe, tailored according to pre-surgical evaluations. Two patients were operated on twice owing to poor results after the first resection. Histology demonstrated a Taylor-type focal cortical dysplasia (FCD) in 16 patients and an architectural FCD in 4. In one case no histological change was found. After a post-operative follow-up of at least 12 months (mean 42.5 months) all the 16 patients with a Taylor's FCD were in Engel's Class Ia and the other 5 patients were in Engel's Classes II or III. After 6 months post-surgery EDS had disappeared in the 9 patients who presented this complaint pre-operatively. It is concluded that patients with drug-resistant, disabling sleep-related seizures of frontal lobe origin should be considered for resective surgery, which may provide excellent results both on seizures and on epilepsy-related sleep disturbances. An accurate pre-surgical evaluation, which often requires invasive EEG recording, is mandatory to define the EZ. Further investigation is needed to explain the possible causal relationships between FCD, particularly Taylor-type, and sleep-related seizures, as observed in this cohort of NFLE patients.

## COMMENTARY

Nocturnal frontal lobe epilepsy (NFLE) is an intriguing disorder. It is more common in males and can present with a variety of behaviors in sleep that are often mistaken for other disorders. Provini et al. divided the seizures of NFLE into three main subtypes, all of which are commonly misdiagnosed as nonepileptic: (1) paroxysmal arousals (with brief but stereotyped motor movements), (2) nocturnal paroxysmal dystonia (with more prolonged asymmetric posturing or dyskinetic/hyperkinetic movements), and (3) episodic nocturnal wanderings (1). The latter tend to involve more agitation and frantic behavior than typical nonepileptic somnambulism. Interictal and ictal EEGs often are unhelpful and nondiagnostic (each about half the time). Family history often reveals relatives with nocturnal spells. Some families seem to have both NFLE and nonepileptic arousals with motor activity or other sleep disorders (2). A number of these minor motor events during sleep are epileptic, as has been proven with intracranial electrode monitoring (3). K-complexes are often present just before or simultaneous with the ictal onset. The familial component led to the discovery of the syndrome of Autosomal Dominant NFLE, which was subsequently linked to a mutation in the gene for the  $\alpha$ -4 subunit of the nicotinic acetylcholine receptor on chromosome 20, though there is genetic heterogeneity.

Overall, NFLE is felt to be rather benign, as seizures are rare or absent during wakefulness; in fact, 17 of the 100 consecutive patients in the series by Provini et al. declined treatment as seizures did not bother them (1). However, their report also noted that only 20% of patients had seizures that were fully controlled on carbamazepine, and 30% were refractory to multiple medications. Furthermore, some patients report having significant sleep disruption because of their nocturnal seizures, with resultant excessive daytime sleepiness. Several studies have shown improvement in sleep with treatment of nighttime seizures (4). Although it has been shown that even daytime temporal lobe seizures can suppress REM sleep the same night (5), it is less clear what the effect of brief diurnal or nocturnal frontal lobe seizures (with minimal postictal state) might be on sleep architecture. However, as Nobili et al. discuss in the article, prior studies have reported that some patients with strictly nocturnal seizures have nonrestorative sleep and daytime somnolence. As sleep quality is related to memory, it is possible that memory also could improve with increased quality of sleep (4). Finally, for patients with uncontrolled convulsions in sleep (which would include some patients with NFLE), there is some evidence that surgical cure may reduce the risk of sudden unexplained death in epilepsy (6).

This study showed excellent surgical results in a selected group of 21 patients with NFLE. During their seizures, most patients had hyperkinetic movements, asymmetric posturing, or both. All but one patient had >20 seizures a month, and

half averaged at least two per night. Only one patient had an autosomal dominant family history. Interestingly, nine patients had somatic sensations with their seizures, some quite localized. Half the patients had focal MRI lesions. Only two patients did not have localizing findings on scalp EEG, showing that the patients in this study were indeed a select subgroup of patients with NFLE who were good surgical candidates and were not representative of NFLE in general. All but three patients had intracranial recordings. Three-quarters of the patients were rendered seizure free, including all 16 with Taylor's type focal cortical dysplasia, three of whom were the ones who did not have invasive monitoring. These findings stress the importance of continued research on MRI identification of focal dysplasia (e.g., multiplanar reformatting, 3D surface rendering, texture analysis, higher field magnets, phased-array coils) and of careful scrutiny of MRIs for subtle cortical thickening with associated blurring of the gray-white junction and increased signal on T2 and FLAIR (7). It remains unclear whether or not patients with clear focal cortical dysplasia on MRI and concordant noninvasive studies also require invasive ictal EEG recordings (and via which type of electrodes). This study does not shed light on this issue.

Nobili et al. made several other important observations. Seizures with asymmetric tonic posturing typically showed early involvement of the supplementary motor area as expected, whereas hyperkinetic seizures involved multiple regions. Fear and nocturnal wandering spells were associated with activation of the anterior cingulate, orbito-polar, and temporal regions. In addition to the excellent results with regard to seizures, the authors also noted resolution of excessive daytime somnolence, including improvement in nine of nine patients with this symptom preoperatively, despite no change in their medication regimen. Although quality of life was not reported, prior investigations have shown that sleep disturbance can be an important determinant of quality of life in epilepsy patients (8).

As reviewed in a recent issue of *Epilepsy Currents* (9), a large series (70 patients) found that poor outcome after surgery for frontal lobe epilepsy, in general, is associated with negative MRI if pathology shows dysplasia, extrafrontal MRI abnormalities, generalized ictal EEG patterns, incomplete resection (defined as incomplete removal of lesion or incomplete removal of lesion plus electrophysiologic abnormalities in those with invasive monitoring), and acute postoperative seizures (10). Those patients with any one of these five unfavorable factors had a low chance of long-term seizure freedom (under 15% at 3 years), but those without any of these factors did well (11/13 or 85% seizure free at 5 years). Nobili et al. now have expanded the profile of the group anticipated to have good outcome after frontal lobe surgery to include carefully selected patients with primarily or exclusively nocturnal seizures, especially those with focal cortical dysplasia and concordant localizing findings on noninvasive evaluation.

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