

NOCTURNAL FRONTAL LOBE EPILEPSY: THERE IS BAD, GOOD, AND VERY GOOD NEWS!

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 a heterogeneous epileptic seizure disorder that affects all age groups. It presents with various clinical manifestations ranging from brief seizures, consisting of stereotypic sudden arousals that recur throughout the night in a periodic pattern, to more elaborate seizures, with complex dystonic and dyskinetic phenomena, or to longer seizures consisting of aimless wandering, simulating somnambulant behavior (1,2). While in most patients NFLE is considered a cryptogenic epilepsy, a familial variant has been identified with an autosomal dominant transmission, known as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) (2,3).

The bad news: NFLE is often misdiagnosed as a sleep disturbance, as it consists of recurrent paroxysmal episodes that occur primarily or exclusively during sleep. The diagnostic confusion often stems from the absence of recorded epileptiform activity in scalp recordings either interictally and/or during the ictal events (1–4). For example, in the largest case series published so far (100 consecutive patients), Provini et al. found an absence of ictal pattern in 44% of patients, while in 51% interictal recordings failed to show any epileptiform discharges. Similarly, in a series of 40 consecutive patients with ADNFLE, Oldani et al. found that a correct diagnosis of epilepsy had been reached in only 18.4% of patients (3).

Unfortunately, there is often reluctance on the part of patients and physicians alike to push for the achievement of total seizure freedom in the 25% to 30% of patients with persistent seizures (1–3). Such complacency results from the assumption that patients can function normally, lead an independent life, and maintain their driving privileges, since the occurrence of seizures is restricted to the sleep state. Yet, contrary to the common belief that NFLE is a benign epilepsy, it is not the case for all patients. Indeed, the persistence of nocturnal seizures has a significant negative impact on the quality of life of these patients because of excessive daytime somnolence, which often can be incapacitating and interfere with patients' school, work, or social activities.

The excessive daytime somnolence results from a seizure-induced sleep disturbance that consists of sleep fragmentation and reduced sleep efficiency. Vignatelli et al. administered a questionnaire on daytime sleepiness-related symptoms and subjective sleep quality to 33 patients with NFLE and 20 controls

(4). Tiredness and spontaneous sleep awakening were significantly more frequent in epilepsy patients than controls (36.4% vs. 11.1% and 50% vs. 22%, respectively). In a study on the macro- and microstructure of sleep in patients with ADNFLE, Zucconi et al. found a relationship between sleep fragmentation as well as nocturnal motor seizures and daytime symptoms (5).

The good news: NFLE can be well controlled with antiepileptic drug (AED) therapy (1–3). For example, in the Oldani et al. series of 40 patients with ADNFLE, seizures had remitted completely in 73% of patients who were administered an AED (3), while in Provini's series, AED therapy remitted seizures in 70% of patients (1). Among the patients with drug-resistant NFLE, surgical treatment is considered a potential option. To date, failure to refer patients in a timely manner for presurgical evaluation and surgery remains an obstacle in the treatment of these patients—an obstacle that can be easily overcome with better patient and physician education. The localization of the seizure focus in NFLE has been facilitated by the significant advances in neuroimaging studies, such as high-resolution MRI with stronger magnets and of functional neuroimaging studies, such as ictal SPECT and subtraction ictal SPECT.

The absence of reported cognitive and behavioral disturbances in patients with NFLE is another item of good news related to this type of epilepsy. Indeed, such disturbances are commonly encountered in other types of frontal lobe epilepsy, including learning disabilities (preceding and/or following the seizure onset), attention-deficit hyperactivity, and impulsivity (6).

The better news: Patients with drug-resistant NFLE appear to be good candidates for surgical treatment, as suggested by the data of the Nobili et al. study. Indeed, the seizure-freedom rates are significantly higher (up to 75%) than those reported in other types of frontal lobe epilepsy surgical series, which have yielded a 40% to 50% seizure-free rate. In a recent study of 70 patients who underwent a frontal lobectomy, Jeha et al. estimated the probability of complete seizure-freedom to be 55.7% (95% confidence interval [CI] = 50–62) at 1 postoperative year, 45.1% (95% CI = 39–51) at 3 years, and 30.1% (95% CI = 21–39) at 5 years (7). The better surgical outcome in NFLE, demonstrated by Nobili et al., was associated with the presence of focal cortical displasias of the Taylor type. Other investigators also have reported favorable postsurgical outcomes following the resection of seizure foci associated with Taylor focal cortical displasia in partial epilepsies that are different from

NFLE. For example, two studies with at least 1-year follow-up found a seizure-free state in 75% and 69% of patients, respectively (8,9). Whether a Taylor FCD is a cause of drug-resistant NFLE is yet to be established.

In conclusion, an investigation of excessive daytime somnolence should be an integral part of each visit in patients with NFLE. When present, it ought to serve as a “red flag,” suggestive of an unsuccessful treatment and of the need to consider further in-depth evaluations to establish the need for alternative pharmacotherapy with AEDs or more aggressive treatments, including surgery.

by *Andres M. Kanner, MD*

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