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Dorsolateral Frontal Lobe Epilepsy

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Abstract

Dorsolateral frontal lobe seizures often present as a diagnostic challenge. The diverse semiologies may not produce lateralizing or localizing signs, and can appear bizarre and suggest psychogenic events. Unfortunately, scalp EEG and MRI are often unsatisfactory. It is not uncommon that these traditional diagnostic studies are either unhelpful or even misleading. In some cases SPECT and PET imaging can be an effective tool to identify the origin of seizures. However, these techniques and other emerging techniques all have limitations, and new approaches are needed to improve source localization.

Keywords

Frontal lobe epilepsy; EEG

1.0 Introduction

The frontal lobe comprises about one third of the human brain. Therefore, it is not surprising that frontal lobe seizures are the second most common seizure. Anatomically, the frontal lobe can be subdivided into three major areas: dorsolateral, medial and inferior orbital. Due to its diverse functions (e.g. motor, language, cognitive and higher brain functions), dorsolateral frontal lobe seizures can present with a range of semiology. Some of these are classic, stereotypic patterns, such as the Jacksonian march associated with seizure originating in motor cortex (York and Steinberg, 2011), others can appear bizarre and suggest psychogenic events. Lateralizing signs may not be present, which can be a diagnostic challenge. In addition, it is not uncommon that investigative studies (e.g. EEG, structural and functional imaging) are non-localizing, or even provide misleading information. This further complicates the presurgical planning of these patients. This review will provide an update of the clinical, diagnostic and therapeutic aspects of dorsolateral frontal lobe epilepsy. Also, we will look at recent advances in the electrophysiology that may assist in better source localization.

2.0 Anatomy and functionality of dorsolateral frontal lobe

Traditionally, dorsolateral frontal lobe can be subdivided into primary motor cortex, premotor cortex and prefrontal cortex. The primary motor cortex is the anatomical area

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composed of Brodmann's area 4 of the precentral gyrus. According to Penfield and Jasper, electrical stimulations applied to the primary motor cortex resulted in localized muscle twitches of the contralateral side of the body in a well organized pattern represented by the homunculus (Penfield and Jasper, 1954). However, evidence also suggested that sensory responses can be elicited by electrical stimulation of the primary motor cortex; while simple motor responses can occur with both precentral and postcentral gyrus stimulations (Nii et al., 1996). Therefore, there can be marked variability or overlap of somatotopic organization. The premotor cortex can be functionally divided into the secondary motor cortex, the frontal eye field and Broca's language area. The secondary motor cortex is located in the lateral portion of Brodmann's area 6. This area is most active during the motor preparation and motor learning (Kaufman et al., 2010 ; Tomassini et al., 2011). The frontal eye fields are located in the region designated by Brodmann's area 8. Cortical stimulation of the frontal eye field mainly produces contralateral, conjugated, saccadic eye movement. This is also commonly followed by contralateral head version (Godoy et al., 1990). Brodmann's areas 44 and 45 represent Broca's language area. This area is thought to be responsible for the language production. Electrical stimulation of this area can produce speech arrest, slowing of speech, anomia, paraphasia, and agraphia (Lesser et al., 1984; Schaffler et al., 1993). Interestingly, Schaffler et al. also demonstrated language comprehension deficits with cortical stimulation of the Broca's area, highlighting the challenge of interpretation of direct brain stimulation for mapping cortex. The dorsolateral prefrontal cortex is the anterior part of the frontal lobe, lying in front of the premotor cortex. This region participates in working memory, emotion processing and executive functions (Ragland et al., 2009; Braver et al., 2010; Neta and Whalen 2011; Ursu et al., 2011).

3.0 Seizure Semiology

Frontal lobe seizures often present a diagnostic challenge. They can be mistaken for nonepileptic events, such as psychogenic behavioral spells, movement disorders and parasomnias. Laskowitz et al. reviewed the clinical characteristics of their experience with frontal lobe epilepsies (Laskowitz et al., 1995). Frontal lobe seizures tend to have early motor manifestation with vocalization, occur during sleep, can cluster and lack of prolonged post-ictal phase. Beyond that, the clinical manifestations of frontal lobe seizures are diverse. Frontal lobe seizures originating in primary motor cortex usually consist of unilateral spreading clonic activity, for example beginning in the face, then spreading to the arm, followed by speech arrest. They are also often characterized by preserved consciousness (Salanova et al., 1995). Versive seizures with forced head turn are often seen in seizures originated from the premotor cortex. These seizures are characterized by involuntary forced head deviation, resulting in sustained and unnatural position of the head. Studies show forced head deviation is contralateral to the frontal lobe seizure focus in > 90% of cases (Wyllie et al., 1986; Janszky et al., 2001). Lateral deviation of the eyes can often be seen, indicative of activation of contralateral frontal eye field. Aphasic seizures may occur if Broca's language area is involved. Prolonged postictal language delay can be seen if the seizure spreads to the dominant temporal lobe (Goldberg-Stern et al., 2004). Seizures coming from the prefrontal cortex have more variable clinical manifestations. Luders et al. classified these seizures as "hypermotor seizures" (Luders et al., 1999). These seizures usually have somatosensory auras followed by bizarre gesture, laughing, shouting, bicycle peddling, and thrashing of the extremities. These hypermotor activities are usually brief in duration, often occur from sleep and may have a very brief post-ictal state (Bancaud and Talairach, 1992; Manford et al., 1996; Luders et al., 1999).

4.0 Diagnostic Imaging

Imaging techniques have been invaluable in the evaluation of seizures. MRI can provide evidence of a structural epileptogenic focus. However, the sensitivity of MRI in detecting lesions in frontal lobe epilepsies has been less than satisfactory. Lawson et al. reported only 12/38 of patients with frontal lobe epilepsies had a lesion, while 16/17 patients with mesial temporal lobe epilepsies had concordant lesions on the temporal lobe (Lawson et al., 2002). Other studies have also demonstrated patients with nonlesional MRI later found to have lesions at the epilepsy surgery (Laskowitz et al., 1995; Lorenzo et al., 1995). Thus, functional neuroimaging has been used as a complement to MRI. In patients with non-lesional MRI frontal lobe epilepsy, FDG-PET is reported to show glucose hypometabolism in 35-60% of cases (da Silva et al., 1997; Hong et al., 2002; Kim et al., 2002). However, the area of hypometabolism can be more widespread than the EEG epileptogenic zone and may include extra-frontal head regions (da Silva et al., 1997). Ictal SPECT is reported to be a more effective means of identifying frontal seizure foci. About 60-90% of patients with frontal lobe epilepsy had ictal SPECT hyperperfusion localized to the ipsilateral frontal region (Stefan et al., 1990; Marks et al., 1992; Harvey et al., 1993; Fukuda et al., 2006).

Subtraction ictal SPECT coregistered to MRI (SISCOM) has been introduced to enhance the utility of ictal SPECT (O'Brien et al. 1998). In a study of extratemporal epilepsy, SISCOM hyperperfusion has high concordance with the epileptic zone identified by scalp EEG, intracranial EEG and MRI (O'Brien et al., 2000). A recent study by Tan et al. reported SISCOM can alter the decision-making and planning process for epilepsy surgery (Tan et al., 2008). The application of statistical parametric mapping (SPM) shows promise for further advancing the role of SPECT in localization of the epileptogenic zone (Kazemi et al., 2010; Brinkmann, et al., 2012; Scheinost et al., 2010).

4.0 Clinical Neurophysiology

4.1 EEG

Long term scalp EEG monitoring is the gold standard for seizure localization. However, interictal EEG of frontal lobe seizures can be non-diagnostic or even misleading. Studies have reported that up to 40% of patients with frontal lobe seizures do not have any interictal discharges (Salanova et al., 1993; Bautista et al., 1998). In a pediatric population study, Lawson et al. showed interictal discharges in frontal lobe seizures can be bilateral synchronous, multifocal, lateralized to temporal lobe, or normal (Lawson et al. 2002). Seizures originating from dorsolateral frontal cortex are more likely to have concordant interictal epileptiform discharges than mesial frontal seizure foci (Bautista et al., 1998; Vadlamudi et al., 2004). This is not unexpected because electrodes placed on the scalp are nearer to the frontal convexity foci, and far from mesial frontal generators. Thus it is also not surprising to find intracranial subdural recording to have a higher sensitivity to detect interictal abnormalities than scalp EEG recording (Salanova et al., 1993).

Ictal EEG onset for frontal lobe seizures can be challenging to interpret due to prominent muscle artifacts from motor activity (see Figure 1), rapid seizure propagation, and the fact that seizures originating from mesial and orbital frontal regions are often not evident of scalp EEG. In addition, compared to temporal lobe seizures, frontal lobe seizures are less likely to have a localized ictal onset on the EEG recording (Swartz et al., 1991; Foldvary et al., 2001). Foldvary et al. reported that while ictal onset of rhythmic theta activity was frequently seen in temporal lobe seizures, the most common patterns for dorsolateral frontal lobe ictal onset were rhythmic epileptiform activity (36%), rhythmic delta (26%), and suppression (14%) (Foldvary et al., 2001). Ictal onset of rhythmic fast activity was also reported in up to 80% of patients whose seizures originated from dorsolateral frontal lobe

region (Bautista et al., 1998). This study also demonstrated the absence of focal electrographic seizure activity nearly excluded the possibility of seizures emanating from dorsolateral frontal head region (negative predictive value of 93%). In addition, a focal ictal beta frequency discharge on scalp EEG was shown to predict excellent outcome in frontal lobe epilepsy surgery. (Worrell et al., 2002). This study showed that the presence of a focal beta-frequency discharge at seizure onset on scalp EEG predicted seizure-free outcome in lesional ($p = 0.02$) and non-lesional ($p = 0.01$) epilepsy patients. At least 90% of patients who had either lesional or non-lesional epilepsy were seizure free if scalp EEG revealed a focal beta discharge at ictal onset. Moreover, logistic regression analysis showed that focal ictal beta pattern and completeness of lesion resection were independently predictive of seizure-free outcome. Only about 1/4 of frontal lobe epilepsy surgical patients had a focal beta-frequency discharge at seizure onset on scalp EEG. However, its presence was highly predictive of excellent postsurgical seizure control.

4.2 EEG-fMRI

Scalp EEG is noninvasive and can be recorded for a long period of time to detect epileptiform discharges. However, only discharges involving large areas of cortex ($\sim 7 \text{ cm}^2$), and in relatively close proximity to the recording electrodes can be correctly localized. Combined EEG and functional MRI (EEG-fMRI) is a new technique showing the hemodynamic effects of interictal epileptiform activity. EEG-fMRI measures changes in oxygenation in response to epileptic events. Studies have demonstrated that local blood oxygen level-dependent (BOLD) signal usually increases in the brain regions corresponding to focal interictal epileptiform discharges (Krakow et al., 1999; Benar et al., 2002). BOLD responses have also been shown to localize the source of spiking activity, even if there are no MRI structural abnormalities (Al-Asmi et al., 2003; Bagshaw et al., 2006; Moeller et al., 2009). BOLD signal changes (positive or negative), however can also occur in areas remote from the presumed epileptic focus (Benar et al., 2002; Al-Asmi et al., 2003; Bagshaw et al., 2004). The mechanisms and clinical implication of these remote activations or suppressions is unclear, but they may identify the underlying epileptic network.

In a recent study by Moeller et al on nonlesional frontal lobe epilepsy, EEG-fMRI was able to localize epileptic foci, which were later confirmed by other functional imaging modalities and pathology (Moeller et al., 2009). Thus, EEG-fMRI shows potential as a tool in the presurgical planning of these complex patients. However, at this stage, the use of EEG-fMRI is not widely applicable. The need to record the EEG in the MR scanner is a technical challenge. Patients must have sufficient interictal discharges to show statistically significant activation during the 30-90 minute MR scanning period.

4.3 High-frequency oscillations

High-frequency oscillations are known to have both physiological and pathological relevance (for a recent review of the clinical relevance to epilepsy see Worrell and Gotman 2011). Gamma frequency oscillations of 30-60 Hz are believed to play a role in learning and memory (Llinas 1988; Lisman and Idiart, 1995). Ripple oscillations between 100-200 Hz are important in memory consolidation (Buzsaki 1989; Buzsaki et al., 1992; Draguhn et al., 2000; Grenier et al., 2001). Evoked potential oscillations of $\sim 600 \text{ Hz}$ have been demonstrated to occur in primary somatosensory cortex during the acquisition of sensory information (Curio 2000). In addition to normal brain functions, high-frequency oscillations ($>60 \text{ Hz}$) have been described at seizure onset (Fisher et al., 1992; Alarcon et al., 1995; Bragin et al., 1999; Spencer and Lee, 2000; Traub et al., 2001; Jirsch et al., 2006; Ochi et al., 2007; Ramachandran et al., 2008; Wetjen et al., 2009) (Figure 2). Studies focused on neocortical epilepsies (Worrell et al., 2004) have demonstrated interictal high-frequency gamma (60-100 Hz) oscillations are highly localized in the seizure onset zone (Figure 3).

More recent studies have extended these results to ripple and fast ripple frequency bands (Blanco et al., 2011). More importantly, these oscillations were uncommon outside the seizure onset zone, supporting that these oscillations are pathological oscillations unique to epileptic brain. Studies have also reported good clinical outcome after resection of epileptogenic zone localized by high-frequency oscillations (Ochi et al., 2007; Ramachandranair et al., 2008; Wetjen et al., 2009; Jacobs et al., 2010; Wu et al., 2010).

Recent reports that high-frequency oscillations can be detected on scalp EEG have stimulated significant interest (Andrade-Valenca et al. 2011). However, recording cerebral generated high frequency activity has well known challenges and pitfalls (Benar et al. 2010). In addition, previous studies using simultaneous scalp and iEEG report approximately 7 cm² of cortex must be involved for the signal to be detected on scalp EEG (Tao et al. 2005). High frequency oscillations tend to be spatially localized, and thus would appear unlikely to be detected on scalp EEG. This is an active area of current research, and should be clarified in the near future.

5.0 Treatment and outcome

Medications remain the first line therapy in treating seizures. In a study on both focal and generalized epilepsies, Kwan et al. reported 47% of patients became seizure free for at least one year with the first drug and additional 13% with the second drug (Kwan and Brodie, 2000). A smaller study on frontal lobe epilepsy showed the combination of valproate and lamotrigine led to seizure freedom for one year in 47% of their patients (McCabe et al., 2001). These patients had previously failed at least three other anti-seizure medications. Thus, valproate-lamotrigine combination could potentially be an alternative therapy in intractable frontal lobe seizures.

There is a consensus that epilepsy surgery should be considered for patients with drug-resistant localization related partial epilepsy. Studies have shown varying degree of seizure-freedom or significant seizure reduction rates of 30-70% after a frontal resection (Laskowitz et al., 1995; Swartz et al., 1998; Mosewich et al., 2000; Kral et al., 2001; Zaatreh et al., 2002; Jeha et al., 2007). It has been well documented that successful surgical outcomes require good localization and delineation of the epileptogenic zone (Mosewich et al., 2000; Worrell et al., 2002; Ochi et al., 2007; Lee et al., 2008; Wetjen et al., 2009). Unfortunately, current standard evaluations of dorsolateral frontal lobe epilepsies are often either nondiagnostic or misleading, making patients with these seizures poor candidates for epilepsy surgery. Recent advances including wide bandwidth electrophysiology to record high-frequency oscillations shows significant promise for improving localization of epileptogenic brain (Worrell and Gotman 2011). EEG-fMRI has been studied, but the technique has its own limitations and will require additional development. Thus, new or improved approaches for localization of epileptogenic brain and treatments are needed for this challenging population.

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1. .

Seizure Onset

2. .

3. .