Epilepsy Research 129 (2017) 59–66

Contents lists available at www.sciencedirect.com

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

The promise of subtraction ictal SPECT co-registered to MRI for improved seizure localization in pediatric epilepsies: Affecting factors and relationship to the surgical outcome

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ARTICLE INFO

Article history:
Received 21 July 2016
Received in revised form
19 November 2016
Accepted 29 November 2016
Available online 30 November 2016

Keywords:
Ictal SPECT
Pediatric epilepsies
Radiotracer injection
Postsurgical outcome

ABSTRACT

Objective: Ictal SPECT is promising for accurate non-invasive localization of the epileptogenic brain tissue in focal epilepsies. However, high quality ictal scans require meticulous attention to the seizure onset. In a relatively large cohort of pediatric patients, this study investigated the impact of the timing of radiotracer injection, MRI findings and seizure characteristics on ictal SPECT localizations, and the relationship between concordance of ictal SPECT, scalp EEG and resected area with seizure freedom following epilepsy surgery.
Methods: Scalp EEG and ictal SPECT studies from 95 patients (48 males and 47 females, median age = 11 years, (25th, 75th) quartiles = (6.0, 14.75) years) with pharmacoresistant focal epilepsy and no prior epilepsy surgery were reviewed. The ictal SPECT result was examined as a function of the radiotracer injection delay, seizure duration, epilepsy etiology, cerebral lobe of seizure onset identified by EEG and MRI findings. Thirty two patients who later underwent epilepsy surgery had postoperative seizure freedom data at <1, 6 and 12 months.
Results: Sixty patients (63.2%) had positive SPECT localizations – 51 with a hyperperfused region that was concordant with the cerebral lobe of seizure origin identified by EEG and 9 with discordant localizations. Of these, 35 patients (58.3%) had temporal and 25 (41.7%) had extratemporal seizures. The ictal SPECT result was significantly correlated with the injection delay ($p < 0.01$) and cerebral lobe of seizure onset (specifically frontal versus temporal; $p = 0.02$) but not MRI findings ($p = 0.33$), epilepsy etiology ($p \geq 0.27$) or seizure duration ($p = 0.20$). Concordance of SPECT, scalp EEG and resected area was significantly correlated with seizure freedom at 6 months after surgery ($p = 0.04$).
Significance: Ictal SPECT holds promise as a powerful source imaging tool for presurgical planning in pediatric epilepsies. To optimize the SPECT result the radiotracer injection delay should be minimized to ≤25 s, although the origin of seizure onset (specifically temporal versus frontal) also significantly impacts the localization.

1. Introduction

More than 750,000 children in the US suffer from epileptic seizures, with approximately 50,000 new cases being diagnosed every year (Russ et al., 2012). Over 30% of these patients do not respond to antiepileptic medications (Berg et al., 2014) and suffer from medically intractable seizures, which are associated with 4–5 times higher morbidity and mortality than that of the generation population (Perucca et al., 2011). There are very few curative treatments for medically refractory epilepsy. Surgical resection of the brain area that is responsible for seizure generation is a treatment option available only to select patients with focal epilepsy. Its success largely depends on accurate localization of the epileptogenic tissue. Eligible patients undergo a complex and extensive preopera-

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http://dx.doi.org/10.1016/j.eplepsyres.2016.11.020
0920-1211/

tive evaluation that includes implantation of invasive electrodes to accurately localize the seizure focus, minimize long-term neurological/cognitive impairment and maximize seizure freedom. Invasive monitoring carries significant risk. To date, there are no sufficiently accurate non-invasive monitoring tools that could optimize, complement and even minimize invasive monitoring, thus reducing the morbidity risk, cost and overall burden of the preoperative evaluation (Duncan et al., 1993; O'Brien et al., 1998).

There is an unmet clinical need for improved noninvasive tools for presurgical evaluation in pediatric epilepsy. Scalp electroencephalography (EEG) remains the primary diagnostic tool in the field and is typically used to guide additional studies. However, its spatial specificity is poor (≥2 cm) and cannot be used by itself for surgical planning. Imaging modalities hold promise for this purpose (Duncan et al., 2016) but have various limitations, particularly in pediatric patients. Magnetic Resonance Imaging (MRI) can only image structural abnormalities potentially associated with seizures or structural changes, such as loss of hippocampal volume that occur as the result of seizures (Barr et al., 1997; Woermann et al., 1998; Briellmann et al., 2002). A substantial number of epilepsy patients have normal MRI scans (Cascino et al., 1991), in which case MRI is not useful for localizing the epileptogenic brain tissue.

Positron Emission Tomography (PET) is a promising modality for imaging changes in cerebral metabolism (hypometabolism) rather than blood flow in the epileptogenic tissue. The more commonly performed interical PET (in contrast to rare ictal PET) has been shown to have good sensitivity (≥70%) to identify the epileptogenic brain tissue as a broad area of hypometabolism (Won et al., 1999; Willmann et al., 2007), but may have limited spatial specificity. Overall, interictal PET has higher specificity in TLE (Won et al., 1999; Kim and Mountz, 2011) and is thus of lesser utility in children given that over 50% of pediatric patients have extratemporal seizures, for whom interictal PET may have lower sensitivity and higher inter-observer variability (Drzezga et al., 1999).

Ictal perfusion Single-Photon Emission Computed Tomography (SPECT) is another promising non-invasive imaging modality that can detect the seizure focus with spatial accuracy that is comparable to that of invasive EEG, but at significantly lower risk to patients (O'Brien et al., 1998; Lee et al., 2000; Van Paesschen, 2004; Treves et al., 2014). Its spatial resolution is 5–10 mm, and thus superior to that of clinical scalp EEG (~2.5 cm) (Ho et al., 1995; Hwang et al., 2001). The minimum amount of brain tissue resected during surgery is typically ~3–4 cm^3, when the seizure focus is precisely localized. Thus, ictal SPECT has sufficiently high spatial resolution to accurately localize the epileptogenic region based on changes in cerebral blood flow (focal cerebral hyperperfusion – see Fig. 1) induced by ictal discharges. Overall, it has higher sensitivity than interictal PET independently of the location of the seizure focus (Kim and Mountz, 2011; Ho et al., 1995; Desai et al., 2013; Perissinotti et al., 2014). Previous studies have shown that ictal SPECT registered to MRI may be valuable for localizing the epileptogenic brain tissue in patients with extratemporal seizures and nonlesional MRI (Perissinotti et al., 2014; Von Oertzen et al., 2011). Given the high incidence of extratemporal seizures in children, ictal SPECT could become particularly useful for surgical planning. However, perfusion may change as seizures propagate and spread to large areas of the brain and thus the sensitivity and spatial specificity of ictal SPECT largely depend on the timing of radiotracer injection. If a seizure is not accurately detected, the radiotracer may not be delivered sufficiently early during seizure evolution in which case SPECT images show diffuse seizure propagation and postictal effects (see Fig. 1) and are of limited clinical utility (La Fougere et al., 2009). Currently, the success rate of ictal SPECT is ~50% but could substantially increase if reliable seizure detection and consequently the radiotracer injection are automated (Shoeb et al., 2004).

The clinical utility of ictal SPECT in children with epilepsy has not been extensively investigated (Vera et al., 1999; Kaminska et al., 2003) and to date it is unclear whether the timing of the radiotracer injection is the primary or sole predictor of its outcome (Lee et al., 2006). Also, only few studies have compared SPECT- and intracranial EEG-based estimates of the epileptogenic region (Kaminska et al., 2003; Thadani et al., 2004; Barba et al., 2007) and/or have assessed the relationship between the epilepsy surgery outcome and the ictal SPECT result. It has been previously shown that concordance between the hyperperfused region in SPECT images and electrocorticography (ECoG) was useful in predicting the long-term postsurgical outcome (Jalota et al., 2016).

In a relatively large cohort of 95 pediatric patients with pharmacoresistant focal epilepsy, this study systematically investigated the ictal SPECT result as a function of multiple potentially affecting factors, including the injection delay, MRI findings and seizure characteristics. The overarching goal of the study was to determine whether the injection delay individually or in combination with other factors predict the SPECT result in pediatric patients who have significantly more heterogeneous seizures than adults. The cohort included 32 patients who underwent epilepsy surgery and had additional information on the postsurgical outcome. The study also investigated the relationship between concordance of the ictal SPECT result, scalp EEG and ECoG with seizure freedom following epilepsy surgery.

2. Materials and methods

2. a Patient cohort

This retrospective study was approved by the Institutional Review Board. Scalp electroencephalograms (EEG), MRI and ictal SPECT images for 95 consecutive pediatric patients with pharmacoresistant localization-related epilepsy and focal onset seizures irrespective of etiology were reviewed (patient records from June 1, 2009 to May 31, 2012 were examined). The only exclusion criterion was epilepsy surgery prior to the ictal SPECT study. Forty eight males and 47 females were included. No patient had repeated studies. Age at imaging was 1–20 years, median = 11 years, (25th, 75th) quartiles = (6.0, 14.75) years. Based on visual examination of scalp EEG at the time of imaging, 38 patients (40%) had frontal lobe seizures, 47 patients (49.5%) had temporal lobe seizures, 8 patients (8.4%) had parietal lobe seizures, and 2 patients (2.1%) had occipital lobe seizures. Magnetic Resonance Imaging (MRI) was available for all patients. Thirty two patients (33.7%) had undergone epilepsy surgery at a later date following the ictal SPECT study.

2. b Ictal SPECT

All patients were first evaluated for the need of sedation, to minimize motion artifacts, and over 50% were sedated prior to ictal SPECT. Nuclear Medicine physicians at our institution are blinded to the EEG findings when reading ictal SPECT studies.

Radiotracer: Tc99m-ECD is the radiotracer almost exclusively used at our institution. In the very few cases when it was not available Tc–99 m HMPAO was used, which typically gives the same results as with Tc–99 m ECD except that it has higher soft tissue uptake in the calvarium. However, this does not affect the diagnosis of focal ictal activity in then cortex on SPECT. Tc99m-ECD is a lipophilic radiopharmaceutical that is rapidly taken up into neurons. Its physical and shelf lives are ~6 h, respectively. Following injection, it takes 15–30 s for the tracer to reach the brain. Its initial distribution is according to the first pass and reflects regional cerebral blood flow. Once taken up by the brain, the tracer is trapped and does not re-distribute to extracerebral regions for hours (Treves