Clinical Neurophysiology 127 (2016) 3301–3305

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Added diagnostic value of magnetoencephalography (MEG) in patients suspected for epilepsy, where previous, extensive EEG workup was unrevealing

Lene Duez [a,*], Sándor Beniczky [a,b], Hatice Tankisi [a], Peter Orm Hansen [a], Per Sidenius [c], Anne Sabers [d], Anders Fuglsang-Frederiksen [a]

[a] Department of Clinical Neurophysiology, Aarhus University Hospital, Aarhus, Denmark
[b] Department of Clinical Neurophysiology, Danish Epilepsy Centre, Dianalund, Denmark
[c] Department of Neurology, Aarhus University Hospital, Aarhus, Denmark
[d] Department of Neurology, Copenhagen University Hospital, Rigshospitalet-Blegdamsvej, Copenhagen, Denmark

ARTICLE INFO

Article history:
Accepted 7 August 2016
Available online 13 August 2016

Keywords:
Magnetoencephalography
Electroencephalography
Epilepsy
Diagnosis
Diagnostic yield

HIGHLIGHTS

- MEG gives an additional diagnostic yield in epilepsy patients where previous EEG failed to do so.
- Specificity remains high after including MEG–EEG in the diagnostic workup.
- MEG should be considered when EEG fails to provide the diagnostically relevant information.

ABSTRACT

Objective: To elucidate the possible additional diagnostic yield of MEG in the workup of patients with suspected epilepsy, where repeated EEGs, including sleep-recordings failed to identify abnormalities.
Methods: Fifty-two consecutive patients with clinical suspicion of epilepsy and at least three normal EEGs, including sleep-EEG, were prospectively analyzed. The reference standard was inferred from the diagnosis obtained from the medical charts, after at least one-year follow-up. MEG (306-channel, whole-head) and simultaneous EEG (MEG–EEG) was recorded for one hour. The added sensitivity of MEG was calculated from the cases where abnormalities were seen in MEG but not EEG.
Results: Twenty-two patients had the diagnosis epilepsy according to the reference standard. MEG–EEG detected abnormalities, and supported the diagnosis in nine of the 22 patients with the diagnosis epilepsy at one-year follow-up. Sensitivity of MEG–EEG was 41%. The added sensitivity of MEG was 18%. MEG–EEG was normal in 28 of the 30 patients categorized as 'not epilepsy' at one year follow-up, yielding a specificity of 93%.
Conclusions: MEG provides additional diagnostic information in patients suspected for epilepsy, where repeated EEG recordings fail to demonstrate abnormality.
Significance: MEG should be included in the diagnostic workup of patients where the conventional, widely available methods are unrevealing.

1. Introduction

Although epilepsy can be diagnosed solely on clinical data, additional investigations are often needed after the first seizure to assess the probability of recurring seizures (Fisher et al., 2014). EEG is one of the most important investigations, which besides supporting diagnosis of epilepsy, also contributes to its classification (Berg et al., 2010). It is well established that in about

Abbreviations: HD-EEG, high density EEG; IEDs, interictal epileptiform discharges; MEG, magnetoencephalography; PNES, Psychogenic Non-Epileptic Seizures; MEG–EEG, simultaneous MEG and EEG; EEG-SD, sleep deprived EEG.

* Corresponding author at: Nørrebrogade 44, Building 10, Parterre, 8000 Aarhus C, Denmark. Fax: +45 7846 3140.
E-mail address: leneduez@aarhus.rm.dk (L. Duez).

http://dx.doi.org/10.1016/j.clinph.2016.08.006
1388-2457/

10–20% of patients with epilepsy, multiple EEG studies including sleep deprived EEG, fail to show abnormalities (Alving and Beniczky, 2009; Salinsky et al., 1987; Browne and Holmes, 2001).

Magnetoencephalography (MEG) records brain activity like EEG, and the two modalities are complementary to each other: MEG is highly sensitive to neural sources that are tangentially oriented to the skull, but, as opposed to EEG, it is almost blind to radial sources (Hämäläinen et al., 1993; Lopes da Silva, 2010). Supplementing EEG with MEG in the diagnostic workup of patients suspected for epilepsy would theoretically have an added diagnostic value and thus be of benefit to the patients.

At present, the main indication of MEG is presurgical evaluation (Bagic, 2016; Bagic et al., 2009), and most of the published evidence on the clinical utility of MEG is about epilepsy surgery (Stefan et al., 2003; Knowlton et al., 2009; De Tiege et al., 2012). MEG is an expensive investigation and is only available at larger centres and therefore seldom used in the diagnostic workup of patients suspected for epilepsy.

The sensitivity of MEG compared to EEG following sleep-deprivation has been investigated in a prospective study that included 51 patients suspected for epilepsy, and who had one normal standard EEG recording in their previous workup. The MEG findings supported the diagnosis in 63% of the cases and sleep-EEG supported the diagnosis in 57% (Colon et al., 2009). MEG was positive in 27 of the 37 patients with epilepsy, and sleep-EEG was positive in 23 of the 37 patients with epilepsy. The added sensitivity of MEG (27-23/37) was 11% when only the patients with a reference diagnosis of epilepsy are taken into account. However, since MEG and sleep-EEG were not simultaneously recorded, a head-to-head comparison is difficult.

The study demonstrated no significant difference in the added diagnostic yield of the two modalities, and the follow-up study after three to eight years, could not demonstrate any difference either (Colon et al., 2016). Since EEG is widely available, and the costs are lower than that of MEG, it is not realistic to assume that MEG will replace sleep-EEG.

However, in 10–20% of patients with epilepsy, even repeated EEG recordings, including sleep-EEG, are consistently normal. In an attempt to elucidate the possible role of MEG in the workup of patients with suspected epilepsy, we hypothesized that in this selected group of patients, MEG will increased the diagnostic yield.

2. Materials and methods

2.1. Patients

Patients were prospectively included from The Department of Neurology, Aarhus University Hospital and The Danish Epilepsy Centre, from April 2011 to June 2015. The inclusion criteria were: (1) paroxysmal clinical episodes, suggesting epileptic seizures; (2) at least three, normal EEG recordings: two EEGs including provocation methods of hyperventilation and photo stimulation and one sleep-EEG recording, without detection of epileptiform abnormalities or pathological slowing. Fifty-two consecutive patients (36 female) were included. Median age was 29 years (range: 16–76). All subjects gave informed consent to the experimental protocol, which was approved by The Central Denmark Region Committee on Biomedical Research Ethics.

Epilepsy is a clinical diagnosis, supported by para-clinical investigation (Fisher et al., 2014). The diagnostic reference standard was inferred from the diagnosis obtained from the medical chart, after at least one year follow-up after MEG. This was based on all available clinical and para-clinical data for each patient, including: description of witnessed seizures, home-video recordings of seizures, neuroimaging, laboratory and neurophysiological data. For 34 patients, long-term video-EEG recordings with the patient́s habitual seizures were available. Psychogenic Non-Epileptic Seizures (PNES) was diagnosed when video-EEG recordings with their habitual seizures indicated non-epileptic seizures.

According to the diagnostic reference standard, 22 patients had the diagnosis epilepsy, at one year follow-up. The remaining 30 patients' seizures were categorized as 'not confirmed epilepsy,' at one year follow-up. In this group of patients, 20 were diagnosed with PNES, based on video-EEG recordings of their habitual seizures; one patient had the diagnosis depression; one had the diagnosis psychosis. One patient was known with epilepsy, but the seizures in question at enrolment in the study were categorized as PNES, based on video-EEG recordings of the current habitual seizures. The remaining seven patients not having confirmed epilepsy at one year follow up, all refused video-EEG, had no treatment with antiepileptic drugs, and had no further seizures in the follow up period.

2.2. MEG and simultaneous EEG

MEG data were acquired at Aarhus University Hospital, Department of Clinical Neurophysiology using a MEG whole-head 306-channel Elekta Neuromag® system with 204 planar gradiometers and 102 magnetometers. Continuous head position indicator was on during the recording. MEG data were pre-processed offline using the spatiotemporal signal space separation (tSSS) method, to suppress the residual interference and to correct for head movements (Taulu et al., 2004; Taulu and Simola, 2006).

Simultaneous EEG data were recorded using a non-magnetic cap (EASYCAP), and additional electrodes covering the inferior part of the head. Forty-two patients were investigated using high density EEG (HD-EEG): 13 patients with 75 electrodes, 12 patients with 60 electrodes, nine patients with 70 electrodes, six patients with 80 electrodes, and three patients with 64 electrodes. Three patients were investigated with an array of 19 EEG electrodes, according to the 10–20 system. Due to large head circumference seven patients were investigated without EEG. Number of electrodes differs due to changing EEG set-up during enrolment period. Additional single electrodes were added for obtaining the electrooculogram. EEG was acquired with a common recording reference. The recording was done on maintenance doses of their habitual antiepileptic drug. If possible, MEG was done during the admission to long term video-EEG monitoring. For all patients, spontaneous magnetic brain activity (eyes-closed, rest, supine position) was recorded for 1 h (sampling frequency 1 kHz; online band-pass 0.1–330 Hz) both for MEG and simultaneous EEG.

The data were offline band-pass filtered 0.5–70 Hz. MEG–EEG was visually inspected by trained physicians (POH, LD, SB) for well-defined interictal epileptiform discharges (IEDs) and slowing, using CURRY 7 Neuroimaging Suite. IED included spikes (20–70 ms) and sharp waves (70–200 ms) (Bagic et al., 2011). Events related to physiological artifacts or rhythms were rejected (Bagic et al., 2011; Fernandes et al., 2005; Ossenblok et al., 2007). MEG was considered of diagnostically added value when it showed clinically relevant abnormalities (epileptiform discharges or abnormal slowing), that previously were not reported (inclusion criterion) and that were not seen in the simultaneously recorded EEG.

3. Results

MEG combined with EEG detected abnormalities (IEDs and slowing), and supported the diagnosis in nine of the 22 patients with the diagnosis epilepsy at one year follow-up, i.e. sensitivity of MEG–EEG was 41%. Abnormalities were seen in both MEG and EEG in three patients, in EEG-only in one patient, and in