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The topographical distribution of epileptic spikes in juvenile myoclonic epilepsy with and without photosensitivity

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HIGHLIGHTS

- Epileptic spikes in photosensitive juvenile myoclonic epilepsy are prevalent in occipital areas.
- The location of the maximum of generalised abnormalities is not affected by photosensitivity.
- There are likely different epileptic networks in photosensitive and non-photosensitive JME.

ABSTRACT

Objective: Up to 30% of people with juvenile myoclonic epilepsy (JME) have photoparoxysmal responses (PPR). Recent studies report on structural and pathophysiological differences between people with JME with (JME+PPR) and without PPR (JME−PPR). We investigated whether electrophysiological features outside photic stimulation differ between these subtypes.
Methods: We analysed EEG recordings of people with JME at a tertiary epilepsy centre and an academic hospital. Photosensitivity was assessed in a drug-naïve condition. We compared the occurrence and involvement of posterior electrodes for focal abnormalities and generalised spike-wave activity in the EEG outside photic stimulation between JME+PPR and JME−PPR.
Results: We included EEG recordings of 18 people with JME+PPR and 21 with JME−PPR. People with JME−PPR had less focal abnormalities in the posterior brain regions than people with JME+PPR (19% vs 55%, $p < 0.05$). There was no difference in the distribution of generalised spike-wave activity between people with JME+PPR and JME−PPR.
Conclusion: This study demonstrates electrophysiological correlates of the previously described structural and physiological differences between JME+PPR and JME−PPR.
Significance: Findings support the hypothesis that posterior interictal EEG abnormalities reflect localised cortical hyperexcitability, which makes patients with JME more sensitive to photic stimuli.

1. Introduction

Juvenile myoclonic epilepsy (JME) is a type of genetic epilepsy characterised by myoclonic jerks shortly after awakening, and generalised tonic clonic seizures. The diagnosis is based on the clinical presentation and confirmed by 3–6 Hz generalised spike-wave (GSW) or polyspike-wave (PSW) activity on the electroencephalographic (EEG) recording. Over a third of people with JME also have absence seizures (Beghi et al., 2006). Focal abnormalities such as

Abbreviations: JME, juvenile myoclonic epilepsy; PPR, photoparoxysmal response; AED, anti-epileptic drugs.

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single spikes, spike-wave complexes and slow waves are seen in 30–45% of cases (Aliberti et al., 1994; Lancman et al., 1994; Seneviratne et al., 2014). At least thirty percent of people with JME also have a photoparoxysmal response (PPR) and myoclonic jerks or generalised tonic clonic seizures triggered by flashing lights (Appleton et al., 2000; Wolf and Goosses, 1986). The PPR is an abnormal response to intermittent photic stimulation. There are four types of PPR: (I) spikes within the occipital rhythm, limited to the occipital regions (II) parieto-occipital spikes with a biphasic slow wave, (III) parieto-occipital spikes with a biphasic slow wave and spread to the frontal region, and (IV) generalised spikes and wave or polyspikes and wave (Waltz et al., 1992). Types (I) and (II) are generally seen as unrelated to epilepsy (Kasteleijn-Nolst Trenité et al., 2001; Waltz et al., 1992). The prevalence of PPR in the general population is estimated around 1.5% (Koeleman et al., 2013). Type (III) and (IV) are considered abnormal. Especially type (IV) appears to be correlated with epilepsy (Kasteleijn-Nolst Trenité et al., 2001). Several recent imaging studies have shown different connectivity patterns in people with JME+PPR and JME−PPR (Bartolini et al., 2014; Vollmar et al., 2012).

We investigated whether the clinical interictal EEG patterns differ between people with JME+PPR type (III) or (IV) and JME−PPR (including PPR type (I) and (II)), by comparing the locations where interictal generalised activity and focal epileptiform abnormalities are seen. We hypothesise that in JME+PPR, there are more interictal EEG abnormalities involving the posterior regions than in JME−PPR.

2. Methods

2.1. EEG selection

We obtained EEG recordings of people with JME, by screening the electronic EEG report databases at Stichting Epilepsie Instellingen Nederland (SEIN), a tertiary referral centre for epilepsy, and at a teaching hospital, University Medical Center Utrecht (UMCU) using the keywords "JME" and the Dutch word for juvenile ("juveniele"). The search encompassed EEG recordings carried out between 1999 and early 2015 at the epilepsy centre and 20102015 at the teaching hospital. The study was approved by the Medical Ethical Committee of the UMCU, which judged informed consent unnecessary as it pertained a retrospective analysis of data collected for clinical purposes. Data were coded for analysis.

Only recordings of people not taking anti-epileptic drugs (AED) were included. Inclusion criteria were: (a) a confirmed diagnosis of JME ("confirmed JME") or a confirmed diagnosis of IGE with a strong suspicion for JME ("probable JME"), based on the EEG or clinical presentation; (b) at least one drug naïve EEG recording available; (c) photosensitivity tested using intermittent photic stimulation, either during the EEG recording that was evaluated for the current study or in a previous EEG recording. Exclusion criteria were: (a) incomplete records; (b) any history of neurological comorbidity that could influence the diagnosis of JME; (c) any MRI abnormalities. Duplicates and reports other than EEG reports were excluded. Clinical information was retrieved from the hospital files.

2.2. EEG recordings and photic stimulation

At SEIN, the 32-channel EEG recordings were recorded at 500 Hz using Stellate Harmonie (Stellate Inc., Montreal, Canada) and a Grass photic stimulator (PS33+, Grass Products, Quincy, Mass., USA) until 2012 and subsequently at a 512 Hz sample frequency with a SystemPlus Micromed EEG system (Micromed SD 16 DC, Treviso, Italy) and photic stimulator (Micromed, Flash 10S Treviso, Italy). The frequencies used for photic stimulation were 2-5-10-15-20-25-30-40 and 50 Hz, with 6-14-16 and 18 Hz added if necessary to determine exact ranges of photic sensitivity. Participants were asked to close their eyes at the same time that stimulation started. At the UMC Utrecht EEGs were recorded using the Micromed Smart Acquisition Module amplifier (Micromed, Treviso, Italy), at a sample frequency of 512 Hz and intermittent photic stimulation was performed using the Micromed stimulator, and additionally the Grass stimulator in cases in which photosensitivity is suspected. Photic stimulation with eyes open was done with 14-16-18-20-25-15-10-5-2 Hz. For 14-16-18 Hz, participants were asked to close their eyes at the same time that stimulation started. The frequencies 20-15-10-5-2 Hz were tested when the participant had their eyes closed. In both centres, electrodes were placed according to the international 10–20 system, with additional electrodes on the ear lobes (A1 and A2). Conventional 10 mm AgAgCl electrodes were used. EEG recording was performed according to the standard clinical protocol, with or without sleep deprivation.

2.3. EEG analysis

After selecting the EEG reports, we retrieved the original EEG recordings. They were re-evaluated by an experienced neurophysiology technician (WS) who was familiar with the reporting style of both centres. The technician was blinded for the research question and assessed the location of focal abnormalities and the location of the maximal amplitude of generalised EEG abnormalities in all EEG recordings. The localised (focal) epileptiform abnormalities outside intermittent photic stimulation or hyperventilation were assessed. Localised abnormalities were defined as paroxysmal focal activity, localised (poly)spike-and-slow-wave activity and (poly)sharp-and-slow-wave complexes. We divided the EEGs into four groups based on the location of the interictal localised abnormalities: No localised abnormalities at all (L−); localised abnormalities present, but not involving the posterior regions (L_{POST-}), see Fig. 1a; localised abnormalities present, also in posterior regions (L_{POST+}), see Fig. 1b; localised abnormalities present only in the posterior regions ($L_{|POST|}$), see Fig. 1c. The EEGs were also divided in terms of the maximum amplitude of generalised or bilateral synchronous discharges outside intermittent photic stimulation as follows: No generalised abnormalities at all (G−); generalised discharges with maximal amplitudes in the anterior regions ($G_{ANT>POST}$), see Fig. 1d; generalised discharges with maximal amplitudes in the posterior regions ($G_{POST>ANT}$); bilateral synchronous discharges without a clear or alternating maximum ($G_{ANT=POST}$), see Fig. 2; bilateral synchronous spike-wave discharges limited to the anterior regions ($G_{|ANT|}$); bilateral synchronous spike-wave discharges limited to the posterior regions ($G_{|POST|}$).

Reports were also divided according to the presence of PPR, defined as an abnormal posterior response spreading to anterior regions (Waltz criteria III or IV) (Waltz et al., 1992). Waltz I and II were included in the JME−PPR group. People were divided into JME−PPR and JME+PPR based on all available EEG reports in which photic sensitivity was tested, so the distinction between JME−PPR and JME+PPR could be based on multiple EEG reports. People with PPR in one report but not in another one were categorised as PPR+.

We compared the number and type of localised discharges (groups L) and the maximum of the generalised SW discharges (groups G) between the JME+PPR and JME−PPR groups.

2.4. Statistical analysis

We compared the clinical characteristics between the people seen at the two centres and between the JME+PPR and JME−PPR groups using Chi^2 test and Fishers exact test. We compared the number of people with JME+PPR and JME−PPR with discharges