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Changes in the frequency of benign focal spikes accompany changes in central information processing speed: A prospective 2-year follow-up study

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ABSTRACT

We prospectively examined whether changes in the frequency of benign focal spikes accompany changes in cognition. Twenty-six children with benign focal spikes (19 with Rolandic epilepsy) and learning difficulties were examined with repeated 24-hour EEG recordings, three cognitive tests on central information processing speed (CIPS), and questionnaires on cognition and behavior at baseline, 6 months, and 2 years. Antiepileptic drug changes were allowed when estimated necessary by the treating physician. At baseline, a lower CIPS was correlated with a higher frequency of diurnal interictal epileptiform discharges (IEDs) and with worse academic achievement. At follow-up, there was a significant correlation between changes in CIPS and EEG changes in wakefulness (in the same direction) when the EEG outcome was dichotomized in IED frequency "increased" or "not increased".
Behavioral problems were more often observed in patients with higher frequency of IEDs in sleep at baseline and in those with ongoing IEDs compared with those with EEG remission (without or with sporadic IEDs in the recording) at the end of the study period. No changes were observed in the results of the questionnaires. A lower diurnal IED frequency at baseline, lack of serial IEDs, and occurrence of only unilateral IEDs were correlated with a higher chance of EEG remission at 2-year follow-up. Electroencephalography remission could not be predicted from other epilepsy variables except from seizure freedom in the last six months. Our results confirm the nonbenign character of 'benign' focal spikes. Whether an early and stable EEG remission can be achieved through antiepileptic treatment and whether this is of benefit for cognitive development should be examined in prospective placebo-controlled randomized trials.

1. Introduction

In children with benign focal epilepsies, highly frequent epileptiform discharges (IEDs), the so called "benign focal spikes", are observed in contrast with infrequent seizures. The same EEG features are also seen in children without seizures [1,2]. Because of reports on cognitive and behavioral problems in relationship to the frequency of IEDs in children with Rolandic epilepsy [3–6], there is an ongoing discussion regarding the significance of the frequency of benign focal spikes on cognition and behavior for an individual child.

In Rolandic epilepsy (RE), the IED frequency first increases. An increasing number of IED foci may be observed as well. When the child grows older, a decreasing frequency is seen until the EEG has completely normalized, which will definitely occur when the child reaches Prepuberty [7,8]. The IED frequency is reflective of the course of the disease activity in combination with changes in brain maturation. It might be a better marker for the disease activity than seizure counts, since seizures are scarce, may be underreported because of nocturnal occurrence or may be suppressed by antiepileptic drugs.

Besides a phenomenon reflecting the disease course, it has been proposed that IEDs might contribute to the cognitive impairment in some of the children. The IEDs may affect cognition acutely but also (additionally) on a more chronic base. Diurnal IEDs in wakefulness in RE have been associated with acute impairment of cognition, but the evidence is scarce. Fonseca [9] observed a significantly higher proportion of errors on a task of discriminating words and pseudowords when spikes occurred between stimulus and response in two patients. The chronic influence of the abundant IEDs on cerebral networks is more often hypothesized as explanation for the cognitive difficulties. A specific vulnerability to IEDs could exist in sleep. Sleep could be important for

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leaning and memory through strengthening of the cerebral network organization [10–12]. Because of the nocturnal increase of IEDs, a relationship of RE with syndromes with ESES (electrical status epilepticus in slow-wave sleep) is suggested [13,14].

Until now, mostly cross-sectional designs have been published, showing correlations between cognitive impairments and a higher IED frequency at one moment in time [3–6]. Also, a correlation between cognitive impairment and background changes (independent of IED characteristics) was published in a cross-sectional design [15]. In this study, we investigated the relationships between EEG and cognition/behavior prospectively. We restricted the EEG analysis to changes in IED frequency. If a decrease of IED frequency was shown to be accompanied by cognitive improvement, this would support the development of controlled intervention trials with cognition and IED frequency as primary outcome measures.

Since our hospital is a tertiary epilepsy center, we included a group of highly affected children who were "at the top of the hill" of their disease course, at the moment of experiencing cognitive complaints in combination with an abnormal EEG and sometimes with refractory seizures as well. To examine cognition, we chose tests that we regard as most "fluid": most prone to quick change, mainly investigating central information processing speed and, in our opinion, the best candidates to show short-term changes in cognition together with IED changes.

2. Methods

The study was approved by the local ethics committee, and all caregivers gave informed consent.

2.1. Inclusion criteria

Twenty-six patients were prospectively included between 2009 and 2012. In our center, it is a standard procedure to perform a 24-hour ambulatory EEG when children are referred due to learning difficulties and epilepsy or due to learning difficulties and interictal epileptiform discharges (IEDs) in an earlier EEG. We included children with learning difficulties from this group if the 24-hour EEG showed IEDs with the characteristics of IEDs seen in benign focal epilepsies [16,17]. Clinical criteria were as follows: IQ > 60, normal MRI, and seizure semiology characteristic of a benign focal epilepsy [18][1] or no observed seizures.

2.2. Clinical follow-up method

Seizure frequency in the year before inclusion was estimated from an interview with the caregivers at inclusion. From inclusion until 2 years of follow-up, caregivers counted seizures prospectively in a diary. Antiepileptic drug changes were allowed when deemed necessary by the treating physician. A dosage increase of at least 25% or starting/adding an AED was considered as reinforcement of the treatment. Seizure changes were determined, comparing each period of 6 months with the previous 6 months (or with the retrospective baseline) and were categorized as follows: remaining seizure-free, became seizure-free, with >50% seizure reduction, with stable seizure frequency, and with >50% seizure frequency increase.

2.3. EEG follow-up method

A 24-hour EEG was repeated at 6 months and at 2 years. Electroencephalograms were recorded with the standard 10–20 electrode positions. From each EEG, 30 random 10-second EEG-pages were collected from a period of 4 continuous hours from the EEG in wakefulness and from the first hour of sleep. To obtain a continuous variable for baseline description/analysis, one viewer (S.E.) counted all seconds containing IEDs in these 30 pages, allowing to calculate the % of IEDs: (number of seconds containing IEDs/300 s) * 100. Because manual IED counts are time-consuming and because a continuous variable does not allow the calculation of significant differences between individual patients, the same pages at baseline and the sets of 30 pages from both follow-up EEGs were scored in four categories by a second viewer (J.B.).[2] Each page was visually categorized as follows: (1) containing no epileptic activity, (2) ≥10–50% of the time, (3) IEDs ≥ 50–80% of the time, or (4) IEDs ≥ 80% of the time. Each second containing 1 or more spike(wave)s was counted as 1 s (10%) of epileptic activity. Intraindividual changes between two sets of 30 category scores from successive EEGs were statistically confirmed by a Mann–Whitney *U* test for repeated measures (alpha < 0.05, two-sided).

EEG improvement/worsening was defined as statistically significant less/more IEDs between two sets of 30 scores for a serial EEG of a patient in wakefulness as well as in sleep. We decided that the EEG in wakefulness and in sleep should be both changed to have a reliable outcome on changes or if without or with sporadic IEDs in wakefulness and non sporadic IEDs in sleep: an unchanged or normalized EEG in wakefulness was required at follow-up together with improvement in sleep for the classification of EEG improvement).

EEG remission was defined as follows: no IEDs or sporadic IEDs (≤3 pages containing an IED within the set of 30 EEG pages) in wakefulness and sleep.

Furthermore, we determined the number or IED foci, unilateral or bilateral occurrence, and presence of ≥6 s of serial spike-wave-complexes.

2.4. Cognition/behavior

2.4.1. Cognitive tests

If there was no recent information available about the intelligence level, the Dutch version of the Wechsler Intelligence Scale for Children — third version was used to measure the intellectual ability of children between the ages of 6 and 16 years at baseline [19]. For two young children, the Dutch version of the Wechsler Preschool and Primary Scale of Intelligence — third version was used [20]. At baseline, 6-month follow-up, and 2-year follow-up (on the day of the EEG registration), the following central information speed processing tests were used:

- The index processing speed from the Wechsler Intelligence Scale.
- The binary choice reaction time measurement, which is a reaction time test with a decision component [21]. The patient has to react differentially to a red square on the left side of the screen and to a green square on the right side of the screen. The reaction time reflects not only the motor speed but also the decision-making process.
- The computerized visual searching task is adapted from Goldstein's visual searching task [21]. A central grid pattern has to be compared with 24 surrounding patterns. Only one of them is identical to the target pattern. The test consists of 24 trails and gives an indication of the information processing speed and perceptual mental strategies. Reaction time, as well as the total number of errors the patients make, is recorded. This task is particularly sensitive to (diurnal) cognitive effects of epileptiform EEG discharges [22,23]. Of each test, a Z-score was calculated, and an average Z-score of the 3 cognitive tests at baseline was computed and compared with the average Z-score at the follow-ups. For individual patients, a difference ≥0.5 between both the average Z-scores was considered to be clinically

[1] Criteria leading to classification of Rolandic epilepsy: focal motor seizures in the sensorimotor facial area and/or hemiclonic or bilateral clonic seizures and EEG with at least a centrotemporal IED focus; other additional focus localizations were allowed. Criteria for Panayiotopoulos syndrome: at least 1 prolonged seizure with the autonomic feature of vomiting/retching or at least 1 prolonged seizure with hypotonia and nonresponsiveness. Additional seizures with eye deviation, visual symptoms, or motor seizures (hemiclonic/bilateral clonic) were allowed. All focus localizations were allowed.

[2] Correlation of the baseline results from the two methods used by viewers S.E. and J.B.: IED wakefulness Spearman: R = 0.96, p < 0.001; IED-score in sleep: R = 0.97, p < 0.001.