Seizure 25 (2015) 80–83

Contents lists available at ScienceDirect

Seizure

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

Attention deficit/hyperactivity disorder and interictal epileptiform discharges: It is safe to use methylphenidate?

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ARTICLE INFO

Article history:
Received 30 September 2014
Received in revised form 5 November 2014
Accepted 3 January 2015

Keywords:
Attention-deficit/hyperactivity disorder (ADHD)
Interictal epileptiform discharges (IED)
Epilepsy
Methylphenidate (MPH)
Antiepileptic drug (AED)

ABSTRACT

Purpose: This study investigated whether interictal epileptiform discharges (IED) on a baseline routine EEG in children with ADHD was associated with the occurrence of epileptic seizures (Sz) or influenced the use of methylphenidate (MPH) during 2 years follow-up.
Methods: A retrospective chart-review of 517 ADHD children with EEG revealed IED in 39 cases. These patients (IED group) were matched on age and gender with 39 patients without IED (non-IED group). We measured at baseline, 1 year and 2 years Sz occurrence, the use of MPH and antiepileptic drug (AED).
Results: At baseline, 12 patients in the IED group had active epilepsy and three of them had Sz during the last year. 36 (92.3%) patients were treated with MPH. Initial positive response to MPH was achieved in 83.3% compared with 89.2% in the non-IED group. At 1 and 2 years follow-up, three patients who also had Sz at baseline and difficult to treat epilepsy, had Sz, without changes in seizure frequency. We found no statistically significant differences between the groups with respect to MPH use at 1 year and at 2 years. Ten patients from IED group, who did not have confirmed epilepsy diagnosis, temporarily used AEDs during the first year of follow-up.
Conclusion: Despite the occurrence of IED, the use of MPH was safe during 2 years follow-up. IED predict the Sz occurrence in children with previous epilepsy, but does not necessarily suggest an increased seizure risk. A caution is warranted in order not to overestimate the significance of temporarily occurrence of IED.

1. Introduction

Interictal epileptiform discharges (IED) on EEG may occur in children with attention deficit/hyperactivity disorder (ADHD) and contribute to the occurrence of ADHD symptoms [1]. ADHD in children is reported to be a risk factor for incident unprovoked seizures and epilepsy [2], and suggested to predispose for epilepsy development as do autism spectrum disorder and cerebral palsy [3–5]. EEGs performed in children with new onset seizures show IED in approximately 18–50%, and IED occurrence is predictive of seizure recurrence, particularly in patients with idiopathic epilepsy [6]. However, the prognostic value of IED in ADHD children with and without previous epilepsy, regarding occurrence of seizure during early illness course, is unknown [7].

Methylphenidate (MPH) is the psychostimulant drug most frequently used for the treatment of ADHD and there is overwhelming evidence for its benefit [8–10]. It is considered to be safe in children without epilepsy. On the other hand, there is limited research about the use of MPH in patients with epilepsy [11–15] and children with ADHD and IED [16]. A recent study found that clinicians appeared to be reluctant to diagnose and initiate treatment for ADHD in children with epilepsy [17]. It is thus of clinical importance whether it is safe to use MPH in ADHD with IED.

The aims of the present study were to investigate whether IED occurrence at ADHD assessment could predict the occurrence of

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http://dx.doi.org/10.1016/j.seizure.2015.01.002
1059-1311/

epileptic seizures (Sz) and influence the use of MPH during 2 years follow-up.

2. Materials and methods

2.1. Participants and procedure

Our study was conducted at Stavanger University Hospital on consecutive patients admitted to assessment during a 6 years period; January 2000–December 2005. We carried out a retrospective chart review of all patients aged 5–14 who were diagnosed with ADHD in accordance with DSM-IV TR [18]. For details see previous publications [7,15]. A digitized 20 min routine awake EEG with 21 electrodes (10–20 system) including hyperventilation and photic stimulation was performed. The EEGs were classified as either epileptiform or nonepileptiform according to the presence or absence of IED. IED were defined as spikes or spike-wave complexes, isolated or occurring serially (in runs) without evident clinical signs of a Sz. The IED index was estimated as percentage of time in three categories (0%, <1%, ≥1%). Sz, epilepsy and epileptic syndromes were diagnosed according to the classification system of the International League Against Epilepsy [19–21]. Sz frequency during the last year was defined as Sz free, 1–12 Sz per year, and >12 Sz per year, and antiepileptic drug (AED) treatment was classified as untreated, monotherapy or polytherapy. We also analyzed data about comorbid disorders of psychological development and IQ level (IQ > 85, IQ < 85).

We were able to carry out EEG at baseline in 517 out of 607 cases (85.4%), and 39 cases (7.5%) had IED. We studied 2 years follow-up of these 39 cases (IED group) and compared them with 39 randomly selected cases matched for age and gender without EA (non-IED group). At baseline, 1 and 2 years we measured the Sz occurrence and frequency, the use of AEDs, and the use of MPH. MPH was administered according to the Norwegian Guidelines [22], in dosage 0.5–1.2 mg per kilo either three times daily (short-acting MPH) or once per day (slow- acting MPH). During titration with MPH the use of AEDs was stable. The response to MPH was evaluated after several weeks of treatment (4–6 weeks). The response was considered positive if significant reduction in ADHD symptoms scores assessed with ADHD IV rating scale was found [23], in addition to parents and teachers observations. During follow-up we registered whether MPH was given or not. In the IED group at least one follow-up EEG was carried out, an additional sleep EEG was performed in 15 cases and long-term video-EEG monitoring in five cases because of diagnostic difficulties (suspect Sz).

2.2. Statistical analyses

Continuous demographic and clinical variables in subjects with and without IED were compared using Student's *t*-tests for continuous and symmetrically distributed data and Mann–Whitney tests for continuous and skewed data. Proportions were compared using Chi-squared test or Fisher's exact test. Methods for matched samples (paired-samples *t*-tests, McNemar's tests) were also applied. However, the application of methods for matched samples did not alter the conclusions. A *p*-value of <0.05 was considered statistically significant.

2.3. Approval

The study was approved by the Norwegian Data Inspectorate and by the Regional Committee on Medical Research Ethics in region West (nr. 010.07). The study was performed in accordance with ethical standards of the Declaration of Helsinki. Written informed consent was obtained from parents.

3. Results

3.1. Demographic and clinical characteristics at baseline

Due to matching procedures there were no differences between the groups regarding age and gender. Proportion of disorders of psychological development or IQ level >85 showed also no differences (Table 1). As reported in previous publications we found that, among the 39 children with IED, 54% had generalized IED, 41% had focal IED, and 5% had mixed IED [7]. The majority 36/39 (92%) of cases with IED had short duration of IED, the IED index was <1%. The IED group had significantly more often predominantly inattentive subtype of ADHD (41%) compared to the non-IED group (15.4%). In the IED group 12 patients had epilepsy with recent seizures (Sz) (last 5 years). During the last year, nine patients were seizure free, two had 1–12 Sz and one had more than 12 Sz. We found that 75% (9/12) had localization-related epilepsy and 25% generalized epilepsy. All patients with epilepsy received AEDs; 10 monotherapy and two polytherapy. No patients in the non-IED group had epilepsy.

At baseline, 36/39 (92.3%) patients with IED were treated with MPH. The three patients that were not given MPH had no previous epilepsy. Initial positive response to MPH was achieved in 30/36 (83.3%) of children with IED; 10/12 (83.3%) of the children with epilepsy and 20/24 (83.3%) of the cases without epilepsy. In the non-IED group of the 37 initially treated cases, 33/37 (89.2%) had positive effect of MPH treatment.

3.2. 1 and 2 years follow-up

At 1 and 2 years follow-up only three patients, all from IED group, had experienced Sz (Table 2). These three patients had pharmacoresistant epilepsy at baseline and had no change in seizure frequency. We found no significant differences regarding the use of MPH. Within the IED group we did not find statistically significant differences between the cases with and without epilepsy regarding use of MPH at 1 and 2 years follow-up (Table 3).

At 1 year follow-up 22 patients in the IED group were treated with AEDs, 12 of them had epilepsy (monotherapy 10, polytherapy two cases). At 2 years 12 children from IED group used AEDs, 10 of them had epilepsy (eight monotherapy, two polytherapy). During follow-up we carried out control EEG in the IED group (one case missing). We found IED in 12 (31.2%) cases; focal in 10 and generalized in 2. In the IED-cases with epilepsy, four cases had only focal IED.

4. Discussion

The main finding of this study was that it seems to be safe to give MPH to patients with ADHD even if they have IED on routine

Table 1
ADHD patients with and without IED at baseline.

Demographics	IED-group ($n=39$)	Non-IED group ($n=39$)	*p*-Value
Age, mean ± SD	9.7 ± 2.7	9.7 ± 2.7	
Gender, female (%)	11 (28.2%)	11 (28.2)	
Developmental disorders	22/39 (56.4%)	17/39 (43.6%)	0.26
IQ >85 (%)	21/38 (55.3%)	23/34 (67.6%)	0.28
ADHD-I (%)	16/39 (41%)	6/39 (15.4%)	0.01
Epilepsy	12/39 (30.8%)	0	
Sz during the last 5 years	12/12 (100%)	0	
Sz during the last year	3/12 (25%)	0	
MPH, at baseline	36/39 (92.3%)	37/39 (94.9%)	0.64
MPH, positive response	30/36 (83.3%)	33/37 (89.2%)	0.47

ADHD-I, ADHD predominantly inattentive subtype; MPH, methylphenidate; IED, interictal epileptiform discharges; IQ, intelligence quotient; Sz, epileptic seizures.