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Frontal-onset absences in children: Associated with worse outcome? A replication study

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ABSTRACT

We studied the clinical and electroencephalographic features in 30 children who were diagnosed with childhood absence epilepsy. According to their EEG pattern we divided the 30 children into two groups: group A: 11 children with classical absences whose ictal EEG showed primary generalized spikes and waves and group B: 19 children with frontal onset of the EEG epileptic abnormalities ('frontal group'). In the frontal group, more frequently complex absences were seen. Although the majority of children responded very well to valproate monotherapy, ethosuximide has to be added in 3 children of the frontal group to achieve seizure freedom. In the frontal group, also more learning and behavioural problems were encountered. This study largely confirms a previous study of Lagae et al. [Lagae L, Pauwels J, Monte B, Verhelle J, Vervisch J. Frontal absences in children. *Eur J Pediatr Neurol* 2001;**5**:243–251]. It seems that frontal onset absences constitute a specific subtype within the childhood absence epilepsies.

1. Introduction

Childhood absence epilepsy (CAE) is an idiopathic generalized epilepsy syndrome, with a strong genetic predisposition, and usually with a favourable outcome.[2,3] Early onset of seizures, rapid and complete response to treatment, and no other seizure types are favourable prognostic factors.[4,5] Almost all children are seizure and drug free in adolescent period, but some of them (20–30%) continue to have absence seizures or develop other types of generalized seizures in later life.[6] The EEG pattern is characterized by a normal background activity with sometimes rhythmic posterior slowing.[7] Ictal discharges consist of generalized, rhythmic, high amplitude spike–wave complexes around 3 Hz (2.5–4 Hz). The frequency is gradually decreasing during the ictal EEG changes to 0.5–1 Hz. In the past decade there are reports focusing on EEG findings in absence epilepsy.[1,8] In these reports, a subgroup of children was identified with focal frontal onset of the ictal epileptic discharges. This subgroup was more difficult to treat, with also more learning problems.[1]

The aim of the present 'replication study' was to determine whether frontal onset of the generalized ictal discharges in children with absence epilepsy indeed is indicative of a more difficult to treat epilepsy.

2. Patients and methods

Basically, the same methodology as described in the paper of Lagae et al.[1] was used as much as possible for this new cohort of children with absence epilepsy:

For inclusion in the study the patients had to fulfill the next criteria:

1. onset of absence seizures before puberty,
2. normal neurological examination,
3. no previous neurological of psychiatric disorder,
4. absences as the initial type of seizure and
5. concordant ictal EEG pattern which is characterized by generalized epileptiform discharges (spike and waves) 3/s on a normal background activity.

In all children a digital EEG was performed using standardized techniques, following the international 10–20 system, with a minimum of 19 electrodes. During recording classical activation procedures were performed: eyes open, eyes closed, hyperventilation (HV) and intermittent photic stimulation (IPS).

We looked at the following clinical parameters in every patient:

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1. age at seizure onset,
2. other type(s) of seizures,
3. average number of seizures per day: we collected these data from medical history and information given by parents,
4. response to treatment: a good response means that the child was seizure free, 4 weeks after the introduction of an adequate anti-epileptic drug (AED),
5. neuro-imaging study (when possible MRI),
6. neuropsychological testing and
7. presence of learning and behavioural problems.

The following data were collected from EEG registration:

1. background activity,
2. posterior rhythmic slowing,
3. duration of the generalized spike and wave discharges periods
4. number of ictal discharges per time unit (average recording time = 25 min),
5. isolated interictal epileptic discharges,
6. focal onset of epileptic discharges as defined by Lagae et al.[1]: initial spikes over the frontal regions, followed by a typical generalized 3 Hz spike and wave pattern,
7. influence of hyperventilation (HV): clinical absence during HV (3 min) and
8. photosensitivity: eliciting epileptiform discharges during intermittent photic stimulation (IPS).

All EEG patterns were interpreted by three neurologists–epileptologists independently. During the actual EEG recording at least one neurologist was present to ensure adequate classification of the seizures.

3. Results

Overall, 30 consecutive children were included in the study. All 30 children (18 girls, 12 boys), aged 4–12 years, were diagnosed with absence epilepsy, according to the International League Against Epilepsy (ILAE) classification criteria.[2] All children have normal clinical and neurological examination, as required in the inclusion criteria. Clinical parameters for both groups are summarized in Table 1.

Eleven patients in our group have belong to group A with "classical" absences (Fig. 1), 19 to group B with "frontal" absences. In the latter group of 19 children with initial frontal epileptic abnormalities, 12 had bilateral frontal onset (Fig. 2a) and 7 unilateral frontal onset (Fig. 2b).

Follow up period was not different among the two groups: average follow up period for group A was 5.3 years (range 1.5–10 years), for group B 5.1 (ranged 1–9.3 years), respectively.

Age at absence onset was similar in both groups. We noted two types of absence seizures: simple absence seizures (staring alone) in 22 patients (10 in group A and 12 in group B) and "complex" absences (staring associated with clear motor phenomena in the face, shoulders or arms) in 8 children. The number of children with complex absences was significantly higher in group B ($N = 7/8$), while in group A there was only 1 child with complex absences.

Regarding other types of seizures there were 2 patients in group A with other seizure types (2 with GTCS), and 1 in B group (1 with GCTS). Frequency of absence seizures was similar for both groups ranging from 5 to 50 (median 15) per day in group A, and from 3 to 35 (median 10) in group B.

All 30 children were treated with valproate as the initial anti-epileptic drug (up to 30 mg/(kg day). If after 2–4 weeks, it became clear that the child was not responding to valproate monotherapy, ethosuximide (ETX) was added to the treatment. Overall, 26 children were on monotherapy after 4 weeks, and in 4 children ETX had to be added. Ethosuximide had to be added in 3 children from group B and in 1 child from group A. After 8 weeks, eventually all children were clinically seizure free. Effective dose of VPA was not different between the two groups.

Neuroimaging was done in 17 patients (7 in group A and in 10 in group B), and in all examined children MRI was normal. Only in two patients (one from both groups) the neuroradiologist marked mild cortical atrophy.

In the group with (unilateral) frontal onset absences, 2 children had behavioural problems and learning disabilities. However, all patients attended normal school, and on formal neuropsychological testing all had an IQ score > 85.

EEG parameters for both groups are presented in Table 2. During the EEG recording at least one period with generalized spike and waves was seen in all patients. In group A the typical generalized epileptiform discharges were recorded 2–7 times per registration, and in group B 1–5 times per registration. Typical ictal EEG recordings from both groups are shown in Figs. 1 and 2. Fig. 1 illustrates a typical group A example. In Fig. 2, a bilateral (Fig. 2a) and unilateral frontal onset absence (Fig. 2b) is shown.

Background slowing was seen in 4 patients from group A and in 12 from group B. Isolated epileptic discharges were recorded in 16/19 children in group B, and in 4/11 in group A. Mean duration of ictal discharges was similar for both groups: in group A 10 s (range 2–20 s) and in group B 10 s (range 3–17 s). During the HV test (before the start of the treatment) all children had a "positive HV test": clinical seizures (absences) were noted by the EEG technician, accompanied by ictal epileptiform discharges of 3 Hz spike and wave complexes.

Photosensitivity was present in two children from group A and in 6 in group B. Photoconvulsive response was not recorded in any patient.

Table 1
Clinical parameters.

Clinic characteristics	Classical absence Group A $N = 11$	Frontal absence Group B $N = 19$ (12 bilateral + 7 unilateral)
Mean age at seizure onset (range) years	6.6 (4–11)	6.4 (3–12)
Follow up period (range) years	5.3 (1.5–10)	5.10 (1–9.3)
Patients with simple absences (N)	10	12
Patients with complex absences (N)	1	7
Patients with other type of seizure	2 GTCS	1 GTCS
Average daily frequency of seizures	15 (5–50)	10 (3–35)
Monotherapy	10 (VPA)	16 VPA
Duo-therapy	1 (VPA + ETS)	3 (VPA + ETS) 2 unilateral F, 1 bilateral F
Neuroimaging	Normal $N = 7$	Normal $N = 10$
Learning disability + behavioural problems	0	2 (unilateral F)