Clinical dissection of childhood occipital epilepsy of Gastaut and prognostic implication


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Background and purpose: Our aim was to describe the clinical and electrical features and the long-term evolution of childhood occipital epilepsy of Gastaut (COE-G) in a cohort of patients and to compare long-term prognosis between patients with and without other epileptic syndromes.

Methods: This was a retrospective analysis of the long-term outcome of epilepsy in 129 patients with COE-G who were referred to 23 Italian epilepsy centres and one in Austria between 1991 and 2004. Patients were evaluated clinically and with electroencephalograms for 10.1–23.0 years. The following clinical characteristics were evaluated: gender, patient age at seizure onset, history of febrile seizures and migraine, family history of epilepsy, duration and seizure manifestations, circadian distribution and frequency of seizures, history of medications including the number of drugs, therapeutic response and final outcome.

Results: Visual hallucinations were the first symptom in 62% and the only manifestation in 38.8% of patients. Patients were subdivided into two groups: group A with isolated COE-G; group B with other epileptic syndromes associated with COE-G. The most significant (P < 0.05) difference concerned antiepileptic therapy: in group A, 45 children responded to monotherapy; in group B only 15 children responded to monotherapy. At the end of follow-up, the percentage of seizure-free patients was significantly higher in group A than in group B.

Conclusions: Childhood occipital epilepsy of Gastaut has an overall favourable prognosis and a good response to antiepileptic therapy with resolution of seizures and of electroencephalogram abnormalities. The association of typical COE-G symptoms with other types of seizure could be related to a poor epilepsy outcome.

Introduction

Childhood occipital epilepsy of Gastaut (COE-G) is a rare epileptic syndrome with an estimated prevalence of 0.2%–0.9% of all epilepsies and 2%–7% of benign...
childhood focal epilepsies [1,2]. It is characterized by brief seizures with visual symptoms, in particular elementary visual hallucinations, illusions or amaurosis. Other occipital symptoms such as sensory illusions of oculomotor movement and ocular pain, tonic deviation of the eyes, eyelid fluttering or repetitive eye closure, as well as complex visual hallucinations, may also occur. Interictal electroencephalography (EEG) often shows occipital spike-wave discharges with fixation-off sensitivity and sleep activation [3,4]. Ictal EEG is characterized by interrupting paroxysms and the sudden appearance of low-voltage occipital waves, fast rhythm and fast spikes [5]. The prognosis of COE-G is still unclear; data from the literature suggest that remission occurs in approximately 50%–80% of patients within 2–7 years from onset, with or without the administration of antiepileptic drugs (AEDs) [1,4,6,7].

In past years, the electroclinical characteristics of COE-G have been described by several studies [6–15], but in the literature there are no studies that have evaluated the response to antiepileptic treatment and the long-term outcome. Moreover, other idiopathic epilepsy syndromes can be associated with COE-G but it is not clear whether this association may or may not affect the long-term prognosis of COE-G.

Therefore, the two main aims of this study were to describe the electroclinical features and long-term evolution of COE-G in a large cohort of patients and to compare long-term prognosis between patients with and without other epileptic syndromes associated with COE-G.

Materials and methods
The long-term outcome of epilepsy was retrospectively analysed in patients with COE-G who were referred to 23 epilepsy centres in Italy and one in Austria. The study included subjects who were observed between 1991 and 2004 and clinically managed in these centres for at least 10 years. The following inclusion criteria for COE-G were applied:

1. visual seizures, such as elementary and complex visual hallucinations, visual illusions, blindness or partial visual loss, sensory hallucinations, and/or deviation of the eyes associated with ipsilateral turning of the head followed or not by impairment of the consciousness and/or hemiconvulsions, generalized tonic-clonic seizures, and migraine-like symptoms;
2. functional occipital spikes or spike-waves reactive or not to eye opening; occipital paroxysms activated by intermittent photic stimulation were also included;
3. normal neurological examination;
4. normal brain imaging.

The classification of other seizures was based on the clinical and EEG findings according to the criteria of the International League against Epilepsy (ILAE) [16].

Criteria of exclusion from the study included personal history of previous brain damage (e.g. intraventricular haemorrhage) or other known causes of epilepsy, such as infections, metabolic and genetic diseases. Patients with typical electroclinical pictures of benign childhood epilepsy with centrotemporal spikes or Panayiotopoulos syndrome from onset were also excluded from this study and followed closely to see whether they showed signs and symptoms of COE-G. In order to exclude mental or neurological deficits, psychological evaluation and psychometric examination were performed in all recruited subjects.

The following characteristics were evaluated: gender, patient age at seizure onset, history of febrile seizures and migraine, family history of epilepsy, duration and seizure manifestations, frequency of seizures and history of medications including the number of AEDs, therapeutic response and final outcome.

Electroencephalography was performed during sleep and wake. Electrodes were placed according to the international 10–20 system. The morphology, topography and reactivity of the interictal discharges to eye closing and opening and intermittent photic stimulation were analysed. Brain computer tomography (CT) scans (20 patients) or magnetic resonance imaging (MRI) (109 patients) were performed in all patients and results were reviewed by a medical doctor blinded for clinical information.

Between 1991 and 2004, 129 patients met the inclusion criteria and were evaluated clinically and with EEG for 10.1–23.0 years (mean ± SD 12.7 years ± 11.3). A mean of 16 ± 6 EEG scans were performed for each patient. Clinical and EEG details of all patients were reviewed and unanimously agreed upon by all authors. Written informed consent was obtained from parents or caregivers of all recruited patients. This study was approved by the Ethical Committee at the University Hospital ‘Santa Maria della Misericordia’ in Perugia, Italy.

Statistical analysis was performed with SPSS Version 16 for Macintosh Computers (Apple Inc., Cupertino, CA, USA). A Fisher’s exact test was used for group comparisons; moreover, the unpaired t test was used. Significance for all analysis was set at P < 0.05.

Results
General clinical features
In this series [129 children, 73 males (56.6%) and 56 females (43.4%)] the age at epilepsy onset ranged
from 8.1 months to 16.2 years, with a mean age of 7.5 ± 6.4 years. Family history was positive for epilepsy in 40 patients (31%). Febrile seizures were reported in 19 patients (14.7%). Psychometric examination was normal in all children. Intelligent Quotient (IQ) levels ranged from 80 to 120 (mean 95).

**Ictal manifestations at the onset of epilepsy**

Elementary visual hallucinations characterized, in particular, by small multicoloured circular patterns in the periphery of a visual field were the first symptom of seizures in 80 patients (62%) and the only ictal manifestation in 50 patients (38.8%). Complex visual hallucinations, described as figures with the same location and movement sequence as in elementary visual hallucinations, were the first manifestation of epilepsy in 49 children (38%) and the only symptom in 19 (14.7%). Nineteen patients experienced acute transient blindness or blurring of vision after visual hallucinations. Visual manifestations were associated with motor seizures in 100 children (77.5%) and were represented, in particular, by deviation of the eyes with ipsilateral turning of the head in 64 patients (64%) and eyelid closure and blinking in 36 (36%).

No patient reported impairment of consciousness following seizures, other types of seizures (e.g. generalized tonic–clonic seizures) or status epilepticus.

Twenty-one children (16.3%) presented migraine symptoms, characterized by mild to moderate headache, associated in some cases with autonomic manifestations (e.g. nausea or vomiting). Duration of migraine ranged from a few minutes to several hours and in five children (23.8%) this symptom accompanied seizures.

Duration of seizures was generally brief (approximately 1 min); seizures occurred whilst awake in all children and frequency ranged from daily to monthly episodes.

**Electroencephalography findings at the onset of epilepsy**

Electroencephalography showed occipital paroxysms in all children: discharges appeared when eyes were closed and decreased or disappeared when eyes were opened in 80 patients (62%); in the remaining cases (49 patients, 38%) EEG showed occasional occipital spikes, non-reactive to eye closure and opening. Intermittent photic stimulation was positive in 53 patients (41.1%) and 44 (34.1%) presented motor seizures following visual manifestations, induced by TV or video games. Occipital discharges were bilateral in 93 patients (72.1%) and unilateral in 36 (27.9%). During sleep, the frequency of occipital paroxysms increased in all patients, but no seizure was recorded. All children presented seizures with clinical and EEG features that demonstrated an occipital lobe origin.

**Antiepileptic treatment**

All patients received AEDs: the most used were sodium valproate (VPA) and carbamazepine (CBZ) amongst the old AEDs, levetiracetam (LEV) and topiramate (TPM) amongst the new AEDs. Other AEDs frequently prescribed were phenobarbital, oxcarbazepine, clobazam, ethosuximide and lamotrigine. Most patients were treated with monotherapy (98 children, 76%), whilst 31 children (24%) required polytherapy or frequent changes of AEDs because of poor seizure control.

**Long-term follow-up**

Duration of follow-up was at least 10 years in all children. During the follow-up, 61 patients (47.3%) presented other types of seizures: in particular, 40 children presented generalized tonic–clonic seizures (GTCS), five developed absence epilepsy (AE) and 16 had focal epilepsy (FE) with secondary generalization. In these patients, follow-up EEG showed the same occipital paroxysms highlighted in the previous one, associated with generalized discharges in 45 patients and focal or multifocal abnormalities in 16 patients. Laboratory tests and neuroimaging studies were repeated (in order to rule out secondary causes of epilepsy) with normal results.

Our patients were subdivided into two groups: group A, 68 children (38 males, 30 females) with isolated COE-G; group B, 61 patients (35 males, 26 females) with other epileptic syndromes associated with COE-G. Between the two groups there were no significant differences in the family history of seizures (positive in 17 patients of group A and in 23 patients of group B) and in the mean age of onset of epilepsy (7.6 ± 6.5 years in group A, 7.2 ± 6.3 years in group B). The most significant difference between the two groups concerned antiepileptic therapy: in group A, 45 children responded to monotherapy; in group B only 15 children responded to monotherapy. Patients from both groups who became seizure-free withdrew antiepileptic therapy after a mean duration of 2.6 ± 1.3 years (range 2.1–3.9 years) and remained seizure-free until the end of follow-up.

**Group A**

Sixty-one children (89.7%) became seizure-free. In these patients, there was an association between the
clinical response to antiepileptic therapy and the improvement of EEG findings: all the children who responded to AEDs showed complete normalization of the EEG. Six patients (8.8%) continued monotherapy, respectively four with VPA, one with LEV and another child with CBZ, and one patient (1.5%) continued polytherapy with CBZ and vigabatrin because of persistent seizures after a first attempt to withdraw antiepileptic therapy. These children continued to present isolated COE-G characterized, in particular, by complex visual hallucinations associated with motor seizures; they did not report other types of seizures.

Group B

Forty-two children (68.8%) became seizure-free and EEG abnormalities disappeared; 19 patients (31.2%) presented recurrent seizures that did not permit the withdrawal of antiepileptic treatment. These patients continued to present typical manifestations of COE-G associated with other types of seizures. Eleven patients (18%) – seven with GTCS, two with AE and two with FE with secondary generalization – continued monotherapy (five with VPA, two with LEV, one with TPM and another child with CBZ). Eight patients (13.2%) – five with GTCS and three with FE with secondary generalization – required frequent changes of AEDs and/or polytherapy. The most used drugs in these patients were VPA, LEV and TPM.

At the end of follow-up, the percentage of seizure-free patients was significantly higher in group A than in group B (group A versus group B, 89.7% vs. 68.8%; \( P < 0.05 \)).

Data about patients of group A and group B are given in Table 1.

Discussion

This is the first large-cohort study that describes in detail the clinical characteristics of epilepsy in patients with COE-G and their long-term outcome and analyses the differences between patients with isolated COE-G and patients with COE-G associated with other epilepsy syndromes, their response to AEDs and their final outcome.

Considering the general clinical features of our patients, some differences were found with previously published data. In particular, in our study the mean age of epilepsy onset is 7.5 years, whilst previous reports assessed that COE-G had a peak of incidence at 8–11 years of age [1,2] and, in a study conducted on 33 patients with this syndrome, the mean age of onset was 8.9 years [6]. Moreover, a slightly higher prevalence of COE-G in males rather than females was found, whilst other studies reported no difference in gender [5,13,17]. Furthermore, ictal or post-ictal migraine has been previously described in about half of the cases of COE-G [6], but in our study less than one-fifth of the patients presented migraine manifestations.

Association of COE-G with other epilepsy syndromes, in particular generalized epilepsy (GTCS, AE) and FE with secondary generalization, has already been reported [6–8,11,18,19], but no study evaluated the long-term evolution of these patients. The results of our long-term follow-up confirm that the overall prognosis of COE-G is good, with complete resolution of seizures and corresponding disappearance of EEG abnormalities in approximately 80% of patients. Seizures can be easily managed with antiepileptic monotherapy: 60 patients (46.6%) obtained seizure freedom with one AED. The most used and effective drugs in both group A and group B patients were VPA, CBZ and LEV. These results are in agreement with previous studies that reported a good outcome of COE-G in 50%–80% of patients and that assessed the efficacy and safety of these AEDs in the management of this type of epilepsy [6–10,15,16]. At the end of long-term follow-up 26 patients (20.1%) presented recurrent seizures and persistence of EEG abnormalities, despite the administration of antiepileptic therapy.

Considering that, during long-term follow-up, approximately one-half of our patients developed other types of seizures, it was decided to clarify whether this association may or may not have influenced the long-term prognosis of epilepsy. When distinguishing between group A and group B patients, it was observed that 19 out of 26 children (73.1%) belonged to group B (12 patients with GTCS, five with FE with secondary generalization and two with AE). In particular, 11 patients required antiepileptic monotherapy and eight required polytherapy and/or frequent changes of therapy, without obtaining resolution of seizures. Therefore, it was hypothesized that the association of typical COE-G symptoms with other types of seizures could be related to poor epilepsy outcome and to drug resistance.

About the other types of seizures associated with COE-G, it was observed that 40 children presented GTCS, 16 had FE with secondary generalization and five had AE. There are very few data in the literature concerning the association of COE-G with other epilepsy syndromes, but some studies have already described the association between COE-G and...
childhood AE and tried to determine whether this relationship is casual or caused by an underlying common mechanism [11,18,19]. Caraballo et al., suggested that the atypical evolution of COE-G may be due to a thalamocortical mechanism and that, when the basal ganglia are activated, absence seizures may be triggered [18–20]. Wakamoto et al., in 2011 [7], found a high rate of patients with GTCS associated with COE-G; they hypothesized that a delay in AED treatment led to secondarily generalized seizures or that all types of motor seizures reported could have been inappropriately described as GTCS.

In agreement with the results of Wakamoto et al. [7], in our study the majority of patients with other epilepsy syndromes associated with COE-G presented generalized epilepsy, in particular GTCS. Thus, it would be interesting to investigate about the possible aetiological relationship between COE-G and other types of seizures, and to conduct other studies in order to determine the real evolution of this association.

Some methodological limitations of our study need to be addressed: because of its retrospective nature, accurate information on seizure frequency and semiology may involve considerable methodological difficulties; there may be a selection bias because the data were acquired from several epilepsy centres.

Thus COE-G has an overall favourable prognosis and a good response to antiepileptic therapy, with complete resolution of seizures and of EEG abnormalities both in patients with isolated COE-G and in patients with other idiopathic epilepsy syndromes associated with COE-G. However, this association could lead to a worsening of the outcome and to the development of drug-resistant epilepsy.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Table 1 Electroclinical features and outcome of epilepsy in 129 patients with COE-G

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group A patients (n = 68)</th>
<th>Group B patients (n = 61)</th>
<th>Total study population (n = 129)</th>
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<tbody>
<tr>
<td>Sex, n (%)</td>
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<tr>
<td>Male</td>
<td>38 (55.9)</td>
<td>35 (57.4)</td>
<td>73 (56.6)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (44.1)</td>
<td>26 (42.6)</td>
<td>56 (43.4)</td>
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<td>Clinical history, n (%)</td>
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<tr>
<td>Family history of seizures</td>
<td>17 (25)</td>
<td>23 (37.7)</td>
<td>40 (31)</td>
</tr>
<tr>
<td>Personal history of febrile seizures</td>
<td>9 (13.2)</td>
<td>10 (16.4)</td>
<td>19 (14.7)</td>
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<td>Seizure onset</td>
<td></td>
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<tr>
<td>Age at onset, years, mean ± SD (range)</td>
<td>7.6 ± 6.5 (0.8–16.2)</td>
<td>7.2 ± 6.3 (1–13.4)</td>
<td>7.5 ± 6.4 (0.8–16.2)</td>
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<tr>
<td>Migraine, n (%)</td>
<td>10 (14.7)</td>
<td>11 (18)</td>
<td>21 (16.3)</td>
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<td>Outcome</td>
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<td>Response to treatment, n (%)</td>
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<tr>
<td>First drug</td>
<td>45 (66.3)</td>
<td>15 (24.6)</td>
<td>60 (46.6)</td>
</tr>
<tr>
<td>Add-on drugs</td>
<td>16 (23.6)</td>
<td>27 (44.3)</td>
<td>43 (33.3)</td>
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<tr>
<td>Intractable epilepsy</td>
<td>7 (10.3)</td>
<td>19 (31.1)</td>
<td>26 (20.1)</td>
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<tr>
<td>Other types of seizures, n (%)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>GTCS</td>
<td>–</td>
<td>40 (65.6)</td>
<td>40 (31)</td>
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<tr>
<td>AE</td>
<td>–</td>
<td>5 (8.2)</td>
<td>5 (3.9)</td>
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<tr>
<td>FE with secondary generalization</td>
<td>–</td>
<td>16 (26.2)</td>
<td>16 (12.4)</td>
</tr>
<tr>
<td>EEG pattern, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Occipital spikes or spike-waves</td>
<td>68 (100)</td>
<td>61 (100)</td>
<td>129 (100)</td>
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<tr>
<td>Generalized discharges</td>
<td>–</td>
<td>45 (73.8)</td>
<td>45 (73.8)</td>
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<tr>
<td>Focal or multifocal discharges</td>
<td>–</td>
<td>16 (26.2)</td>
<td>16 (26.2)</td>
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<td>Follow-up duration, years, mean ± SD (range)</td>
<td>12.5 ± 11.2 (10.2–23)</td>
<td>12.8 ± 11.4 (10.1–16)</td>
<td>12.7 ± 11.3 (10.1–23)</td>
</tr>
<tr>
<td>Age at last follow-up, years, mean ± SD (range)</td>
<td>16.2 ± 15 (12.1–33.5)</td>
<td>17.6 ± 16.2 (11.2–40)</td>
<td>17.5 ± 16.1 (11.2–40)</td>
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<tr>
<td>Seizure-free at last follow-up, n (%)</td>
<td>61 (89.7)</td>
<td>42 (68.8)</td>
<td>103 (79.9)</td>
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<td>Therapy at last follow-up, n (%)</td>
<td></td>
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<tr>
<td>No therapy</td>
<td>61 (89.7)</td>
<td>42 (68.8)</td>
<td>103 (79.9)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>6 (8.8)</td>
<td>11 (18)</td>
<td>17 (13.2)</td>
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<tr>
<td>Polytherapy</td>
<td>1 (1.5)</td>
<td>8 (13.2)</td>
<td>9 (6.9)</td>
</tr>
</tbody>
</table>

COE-G, childhood occipital epilepsy of Gastaut; GTCS, generalized tonic–clonic seizures; AE, absence epilepsy; FE, focal epilepsy; EEG, electroencephalography.
References


