Childhood epilepsy with occipital paroxysm: classification, atypical evolution and long-term prognosis in 35 patients

Ayşe Aksoy[1,2], Göknur Haliloğlu[1], Dilek Yalnızoğlu[1], Güzide Turanlı[1]

Division of Pediatric Neurology, [1]Department of Pediatrics, Hacettepe University Faculty of Medicine, and [2]Dr. Sami Ulus Children's Hospital, Department of Pediatric Neurology[2], Ankara-Turkey. E-mail: aysechild@gmail.com

Received: 14 July 2015, Revised: 16 September 2015, Accepted: 14 October 2015

SUMMARY: Ayşe Aksoy, Göknur Haliloğlu, Dilek Yalnızoğlu, Güzide Turanlı. Childhood epilepsy with occipital paroxysm: classification, atypical evolution and long-term prognosis in 35 patients. Turk J Pediatr 2015; 57: 439-452.

We studied childhood epilepsy with occipital paroxysms (CEOP) with regard to typical and/or atypical ictal symptoms, EEG findings, as well as atypical evolution and outcome. This report focuses on the main clinical and EEG features of CEOP underlying its atypical symptoms and its management. Thirty-five patients with CEOP were subdivided into Panayiotopoulos syndrome (n=15), Gastaut syndrome (n=11), and mixed type (n=9). Nine patients (25%) with CEOP (mixed type) had shown atypical ictal manifestations and presented combinations of vomiting (100%) along with visual symptoms (66%), and/or eye deviation (66%), and headaches (44%). Five patients with CEOP had atypical evolution. However, the dictate for strict delineation into either the early-onset or late-onset forms of CEOP should be discarded because many children will present mixed clinical findings at varying ages. We think a detailed evaluation should be carried out as to why certain patients who apply have atypical findings, and whether each patient has age related evolution or not.

Key words: occipital lobe epilepsy, atypical evolution, outcome.

Childhood epilepsy with occipital paroxysms (CEOP) are mainly two distinctive electroclinical sydromes: Panayiotopoulos syndrome (PS), an autonomic epilepsy that is common and idiopathic childhood occipital epilepsy of Gastaut (G-CEOP) that is rare and of uncertain prognosis.[1,2]

Panayiotopoulos syndrome is a childhood-related syndrome rendering patients susceptible to autonomic status epilepticus and has been redefined by the ILAE.[1,3] Onset is commonly between the ages of 3-6 years (76%) and usually presents infrequent and lengthy seizures that mainly occur in sleep (70%). PS is characterized by non-visual symptoms including tonic head and eye deviation, ictal vomiting and seizures with or without partial status epilepticus. Seizures can vary in duration from a few minutes to hours. Interictal electroencephalograms (EEGs) shows great variability in that spikes may appear, mainly multifocal, anywhere. Occipital spikes predominate but these do not occur in a third of patients. [4,5]

Gastaut type idiopathic childhood occipital epilepsy (G- CEOP) is characterized by brief and frequent seizures with mainly visual symptoms, such as elementary visual hallucinations, illusions, or amaurosis, followed by hemiclonic seizures while awake. Ictal or postictal headaches occur in half of the patients. Age at onset ranges from 3-15 years, with a peak at 8-11 years. Interictal EEGs reveal spikes sharp and slow wave paroxysms in occipital regions.[4,6]

The diagnosis of seizure symptomatology distinguishing PS from G- CEOP is important, and may overlap. Past studies have strongly suggested that this is an erroneous view and that the two types are likely to be separate disorders, rather than variants of a single disorder. Although seizures in G- CEOP are indeed likely to originate in the occipital lobes, this is unlikely to always be the case in PS.[3,7,8] It has been reported that a large series of children with CEOP, of whom 18% had multiple visual symptoms and fulfilled the rigid criteria for G-

CEOP, 54% presented clinical manifestations compatible with PS, and the rest had a mixture of signs and symptoms of both distinctly defined syndromes.[9,10] Furthermore, atypical evolutions of CEOP have been repeatedly recognized.[11] Recently some studies recently have reported that this variant of CEOP and benign idiopathic partial epilepsy can appear in the same patients either at the same or at different times.[11-14]

Based on the differences in prognosis, it is important to distinguish PS from G- CEOP in clinical practice. The main purpose of this study was to determine the ictal manifestations of the diagnosis of PS and G- CEOP and to identify clues from clinical and EEG findings that can be used to predict the outcome. As a secondary aim, the overlap between the subgroups' defined syndromes was evaluated. We have analyzed the differences in atypical clinical presentations and atypical evolution, response to antiepileptic drugs (AEDs), prognosis among these subtypes, and description of the mixed type.

Material and Methods

Our study population included patients with ICOE retrospectively evaluated between January 1999 and January 2012 in Hacettepe University İhsan Doğramacı Children's Hospital, Department of Pediatric Neurology, a tertiary referral centre. We selected patients with clinical and/or EEG features indicating occipital lobe involvement. From 50 patients with CEOP, 35 patients fulfilled the criteria for the present study (15 patients were excluded due to incomplete follow-up). This study was approved by the ethical committee of the İhsan Doğramacı Children's Hospital, and written informed consent was obtained from all patient's families.

We analyzed gender, age at seizure onset, seizure frequency and duration, seizure semiology, circadian distribution, history of febrile seizures/epilepsy and migraine, therapeutic response, EEG findings and outcome. The semiology of seizures, such as impairment of consciousness, ictal behavioral disturbances (crying, fearing), vacant spells, visual symptoms, eye deviation, headache and vomiting were assessed according to the medical records and detailed re-interview with parents by telephone or in certain cases with seizure-video-records.

The patients were classified as 'PS' if ictal semiology included at least five of the following features: a) onset in early childhood to early adolescence (range: 1-14 years), b) predominantly nocturnal seizures (> 2/3 attacks), c) autonomic features (sweating, malaise, nausea, retching, pallor or flushing), d) ictal vomiting, e) impaired consciousness, f) longer duration (>3 min or >30 min – 1 hour), g) rare seizures (1-15 in total) and h) follow-up examinations for longer than 2 years.[2, 15] If patients had additional initial visual symptoms and post-ictal headache, they were included in the 'mixed group'.[16] Patients were classified as 'G-ICOE' if ictal semiology included at least five of the following features: a) onset in childhood to mid-adolescence (range: 3-15 years), b) diurnal (> 2/3 attacks), c) brief (seconds to a minute) and frequent (usually >15 in total) seizures, d) prominent initial visual hallucinations, e) ictal blindness, f) post-ictal headache and g) follow-up examinations for longer than 2 years. [2, 15] If the patients had additional initial ictal vomiting, they were included in the 'mixed group'.[16]

Awake and asleep EEG recordings were classified according to whether occipital spikes were unilateral or bilateral and/or with the presence of slowing or normal background activity, reactivity to eye opening, and extra-occipital spikes. Lack of occipital paroxysms did not exclude the definition of occipital lobe epilepsy based on typically reported clinical manifestations. Initial EEG was performed in all cases within 24 h from the first seizure. AEDs were administered in all cases, except in one patient with mixed type and changed according to the clinical and EEG evolution. Remission and duration of the seizure-free period in untreated patients or after discontinuation of treatment were evaluated.

Statistical analysis

Demographic data, ictal symptoms, EEG, MRI, response to treatment, and duration of epilepsy were compared using chi-square test or Mann-Whitney U test, with values of $p<0.05$ considered as significant.

Results

a. Sex and age at onset of seizure

Among the 35 children included in the analysis, girls (60%) were found to predominate. Age at onset of seizure was from 1 to 12 years 6 months (mean ± SD, 6.2 ± 3.4). The characteristics and demographic findings of the 35 patients are described in Table I. The 35 children with CEOP were further subdivided into PS, G- CEOP and mixed group. The mean age at the time of the first seizure differed in the three groups of CEOP. The characteristic findings of the three groups are described in Table II.

Statistical analysis failed to identify any significant difference regarding family history of seizure, number of recorded EEG, years of follow-up, and prognosis between patients.

b. Seizure type and syndrome classification

The most common ictal symptom was vacant spell (91%). Impairment of consciousness (83%), autonomic disturbances (74%) and eye deviation (69%) were the second most common ictal symptoms (Table IV).

In the PS group, the most common ictal symptom was impairment of consciousness (100%). Vacant spells (93), eye deviation (87%), vomiting (80%), and autonomic disturbances (80%) were the second most common ictal symptoms. Twelve patients (80%) presented autonomic disturbances at the onset or during the course of the seizure. Autonomic manifestations were relatively common, usually as the seizure progressed. These were incontinence of urine (33%), pallor (30%), perioral cyanosis (20%), hypersalivation (20%) and midriasis (15%). Nine patients (60%) had less than four seizures; four of these (27%) had a single seizure. Six patients (40%) had more than four seizures. Overall, 53% of the patients had exclusively nocturnal seizures. Thirteen patients (86%) had prolonged seizures (> 3 minutes), 6/13 (40%) had convulsive status epilepticus (all of them had generalized tonic-clonic seizures). The incidence of status epileptics was higher in PS, accounting for 40 %. Seizure-free intervals of one year or longer were observed in 13 patients (87%) (Table IV).

In the G-CEOP group, the more common ictal symptoms were vacant spells (82%),

Table I. Demographic Characteristics of CEOP

Characteristics	CEOP (n=35)
Number (male/female, %)	35 (14/21, 40/60)
Age at first seizure Range, years and months (Mean ± SD, years)	 1 yr-12 yr 6 mo (6.2 ± 3.4)
Hx febrile seizure, n (%)	8 (23)
Family history, n (%)	
FHx epilepsy	11 (31)
FHx febrile seizure	7 (20)
FHx migraine	5 (14)
Treatment, n (%)	
No AED	1 (3)
One AED	29 (83)
Two AEDs	5 (14)
Three or more AEDs	0
Discontinuation of AED	10 (29)
Prognosis Seizure-free, n (%)	 29 (83)
Years of follow-up Range, years and months (Mean ± SD, years)	 2 yr - 12 yr (5.23 ± 2.46)

AED: Antiepileptic drug, CEOP: Childhood epilepsy with occipital paroxysms
FH: Family history, Hx: History, SD: Standard deviation

Table II. Clinical Features and Demographic Characteristics of Early-Onset (Panayiotopoulos Type), Late-Onset (Gastaut Type) and Mixed Type

Characteristics	Panayiotopoulos n (%) 15(43)	Gastaut n (%)11 (31)	Mixed n (%) 9 (26)
Number (male/female)	15 (7/8)	11 (4/7)	9 (3/6)
Age at first seizure			
Range, years and months	1 yr - 10 yr	3 yr - 14 yr (7.95	4 yr – 11 yr
(Mean ± SD, years)	(4.25 ± 1.76)	± 3.93)	(7.38 ± 1.06)
Hx febrile seizure, n (%)	4 (29)	2 (17)	2 (22)
Family history, n (%)			
FHx epilepsy	6 (40)	2 (18)	3 (33)
FHx febrile seizure	2 (13)	3 (36)	2 (22)
FHx migraine	3 (20)	1 (9)	1 (11)
Ictal symptoms, n (%)			
Impairment of consciousness	15 (100)	7 (64)	7 (78)
Secondary generalized seizure	11 (73)	4 (36)	7 (78)
Focal motor seizure	3 (20)	5 (45)	1 (11)
Eye deviation	13 (87)	5 (45)	6 (67)
Head deviation	10 (67)	5 (45)	6 (67)
Vacant spell	14 (93)	9 (82)	9 (100)
Ictal behavioral disturbances	9 (60)	6 (55)	4 (44)
Autonomic disturbances	12 (80)	3 (27)	7 (78)
Visual symptoms	0	7 (64)	6 (67)
Positive	0	3 (27)	4 (44)
Negative	0	4 (36)	2(22)
Headache	0	7 (64)	4 (44)
Ictal	0	5 (45)	2 (22)
Postictal	0	2(17)	2 (22)
Vomiting	12 (80)	0	9 (100)
Ictal	6 (40)	0	9 (100)
Postictal	6 (40)	0	3 (33)*
Circadian distribution, n (%)			
Nocturnal only	8 (53)	0	3 (33)
Diurnal only	5 (33)	6 (55)	5 (56)
Nocturnal and diurnal	2 (13)	5 (45)	1 (11)
Status epilepticus (convulsive)♯	6 (40)	0	2 (22)

*Three of mixed type patients had both ictal and postictal vomitting

♯ generalized tonic-clonic seizure

impairment of consciousness (64%), visual hallucinations (64%) and headache (64%). Seven patients (64%) had visual hallucinations, including four (36%) who had ictal blindness, and three (27%) who also had positive visual hallucinations, accompanied by versive manifestations in five patients (45%). The remaining two patients had visual symptoms without versive manifestations. Seven patients (64%) presented headache at the onset or during the seizure. In five (45%) of them, the headache was followed by impairment of consciousness with (n=3) or without (n=2) evolution to generalized seizures. Six patients (55%) had more than four seizures and occurrence of seizures while awake. No

patients had only nocturnal seizures. (Table II).

In the mixed group, there were nine patients. Their clinical features resembled PS type with respect to the early onset of seizures (median: 7 years 6 months), early remission (9 years 6 months), low recurrence rate (only 22% had more than 4 seizures). The most common ictal features were ictal vomiting and vacant spells (100%), and other common ictal features were autonomic disturbances (78%), impairment of consciousness (78%), visual symptoms (67%) and head deviation (67%) (Table II). Seven patients (78%) had seizures ending with generalized convulsions only during sleep. Interestingly, our mixed group had a symptom overlap; patients presented combinations of vomiting (100%) along with visual symptoms (67%), and/or eye deviation (67%), headaches (44%), and five patients (56%) with eye and/or head deviation that accompanied and followed visual hallucinations. Seizure-free intervals of one year or longer were observed in 8 patients (89%) (Table IV).

c. Electroencephalographic findings

Routine EEG included waking records. Sleep EEG was obtained when waking records revealed no occipital paroxysms, or when the patients showed poor cooperation during the recording while awake. The number of EEGs during follow-up ranged between 2-10 for each patient (total EEG number: 147), with a mean of 3.7 records (SD: 2.7). Interictal EEGs revealed normal background activity for all patients. In 12 patients (34%), occipital paroxysms were present during wakefulness, in 40% during sleep and in 26% during both wakefulness and sleep. Ictal EEGs were not recorded. Two (6%) patients with typical clinical features of CEOP had completely normal EEGs

Table III. Clinical Features and Semiologic Findings of CEOP

Characteristics	CEOP (n=35)
Ictal symptoms, n (%)	
Impairment of consciousness	29 (83)
Secondary generalized seizure	22 (63)
Focal motor seizure	9 (26)
Eye deviation	24 (69)
Head deviation	21 (60)
Vacant spell	32 (91)
Ictal behavioral disturbances	19 (54)
Autonomic disturbances	26 (74)
Visual symptoms	13 (37)
Positive	7 (53)
Negative	6 (7)
Headache	11 (31)
Ictal	7 (20)
Postictal	4 (11)
Vomiting	21 (60)
Ictal	15 (43)
Postictal	6 (17)
Circadian distribution, n (%)	
Nocturnal only	11 (31)
Diurnal only	15 (43)
Nocturnal and diurnal	8 (23)
Status epilepticus (convulsive) ♯	8 (23)

♯ generalized tonic-clonic seizure

despite two or five repeated recordings per patient performed during sleep and wakefulness (One of G- CEOP and mixed type) (Table V). Their last EEG was performed from 6 months to 4 years.

In the present study, 33 patients (94%) had spike and sharp waves in the initial interictal EEGs (occipital with/without extra-occipital), while two patients (6%) had normal findings during both awake and sleep EEG, and one patient (3%) had only extra-occipital foci (Table IV). Reactivity to eye opening was assessed in 22% of the patients. In our study, the initial EEG recording showed interictal epileptiform discharges localized in the occipital lobe in 89% of patients. During follow-up, interictal epileptiform discharges were localized to the occipital lobe in 49% of patients (Table V).

Only occipital spike-and wave complexes or small-amplitude occipital spikes were performed in 93% of PS, 91% of G- CEOP and 89% of mixed type in the initial interictal EEGs. Then, final EEG features, in 60% of PS, 36% of G-CEOP and 33% of mixed type were performed occipital spikes. Extra-occipital spikes, all with the benign morphology of high-voltage spikes often followed by slow waves, were found in one (3%) of 35 children who was PS in the initial EEGs. Three patients (9%) showed extra-occipital discharges in their follow-up EEGs (two of the PS and one of the mixed type) (Table V). Most of the extraoccipital foci were mid temporal, sentro-temporal or parietal; the remaining were frontal.

According to initial EEG features, in five patients (14%) the epileptiform discharges were exclusively secondary generalized; in 4 of the 5 patients in the PS group, the remaining one patient in the G-CEOP group. Then, final EEG features: in four patients (11%) the discharges were exclusively secondary generalized; in 2 of the 4 patients in the mixed, one patient in the G-CEOP and one patient in the PS group. All of them occurred only during sleep. There were no statistical differences between patients with or without interictal abnormalities with regard to the age of onset, duration of the first seizure, or the recurrence of seizures.

EEG evolution; 15 patients with abnormal EEGs were followed up until normalization of their records, which occurred at age 1 to 14 years (mean; 4.5 years) and from 1 to 6 years (mean; 2.6 years) after their last seizure. These children were found in six (40%) of the PS, six (54%) of the G-CEOP and three (40%) of the mixed type, but four of them also had

Table IV. Main Differences Among Early-Onset (Panayiotopoulos Type), Late-Onset (Gastaut Type) and Mixed Type

Characteristics	Panayiotopoulos (n=15)	Gastaut (n=11)	Mixed (n=9)
Seizure duration, n (%)			
< 1 min	2 (13)	8 (73)	1 (11)
> 3 min	7 (47)	3 (27)	6 (67)
≥ 30 min to hour	6 (40)	0	2 (22)
Number of seizures: >4 seizures, n (%)	6 (40)	6 (55)	2 (22)
Treatment, n (%)			
No AED	0	0	1(11)
One AED	13 (87)	7 (64)	7 (78)
Two AEDs	2 (13)	4(36)	1 (11)
Three or more AEDs	0	0	0
Discontinuation of AED	4 (27)	3 (27)	3 (33)
Prognosis			
Seizure-free, n (%)	13 (87)	8 (73)	8 (89)
Years of follow-up Range, years and months (Mean ± SD, years)	2 yr - 10 yr (4.73 ± 2.43)	3yr-7yr (5.00 ± 1.73)	3yr- 12 yr (6.33 ± 3.12)

AED: Antiepileptic drug

seizures (two of the PS, one of the G-CEOP and the mixed type).

On the final examination, 8 of 35 patients (23%) showed shift from the occipital to frontal, parietal, temporal or central locations alone or in various combinations (shifted to the frontal, parietal, or temporal regions in 4 patients with mixed type (44%), three of them also had occipital regions, and 4 patients with PS (27%) frontopolar, temporal or central). None of the patients with G-CEOP showed migration.

In the mixed group, 89% of patients were determined to have occipital abnormalities in the initial EEG recordings. In 33% of these patients, there were EEG abnormalities on the final recording, with a mean of 5.0 ± 2.1 years after their last seizure. One patient still had seizures (Patient 5, Table VI).

d. Treatment and follow-up

Thirty-four patients (97%) received antiepileptic drug (AED); 6 patients (17%) had recurrent seizures (four of them in the PS and two in the mixed type). 29 patients (83%) received one drug (41% received valproate, 24% carbamazepine, 24% oxcarbazepine, while the others received topiramate, clonazepam, or levetiracetam). Five patients (14%) received two drugs, and one patient with mixed type (3%) received no AED as spontaneous remission was observed (Patient 4; Table VI). During follow up, in 10 of 35 (29%) patients, treatment was eventually discontinued, but five of them (50%) stil had EEG abnormalities. In terms of achieving control, the mixed and PS syndromes in our study were easier to control than G-CEOP, and required two AEDs, yet their long-term prognosis was still good.

We found that 29 of 35 (83%) patients became seizure-free while 16 (%55) patients still had epileptic activity (occipital with/without extra-occipital) and there was no difference among the G- CEOP subgroups in terms of becoming seizure-free [nine with the PS(87%), three with G-CEOP (73%), four with mixed type (89%), Table V]. Moreover, all patients had reached seizure remission at 37 months (PS), 44 months (G-CEOP) and 43 months (mixed type); in other words, the active disease duration

Table V. Follow-Up EEG Findings of Early-Onset (Panayiotopoulos Type), Late-Onset (Gastaut Type) and Mixed Type CEOP

Characteristics	Panayiotopoulos (n=15)	Gastaut (n=11)	Mixed (n=9)
First EEG, n (%)			
Abnormal background	0	0	0
Occipital spikes	14 (93)	10 (91)	8 (89)
Unilateral (n, right/left, %)	4 (27)/2 (13)	4 (36)/ 4 (36)	3 (33)/2 (22)
Bilateral	8 (53)	2(18)	3(33)
With extra-occipital spikes	4 (27)	1 (9)	1 (11)
With secondary generalized discharges (only asleep)	4 (27)	1 (9)	0
Extra-occipital spikes only	1 (7)	0	0
Normal	0	1 (9)	1 (11)
Last EEG, n (%)			
Abnormal background	0	0	0
Occipital spikes	9 (60)	4 (36)	3 (33)
Unilateral (n, right/left, %)	4 (27)/2 (13)	1 (9)/3 (27)	1 (11)/1 (11)
Bilateral	3 (20)	0	1 (11)
With extra-occipital spikes	2 (13)	0	2 (22)
With secondary generalized discharges (only asleep)	1 (7)	1 (9)	2 (22)
Extra-occipital spikes only	2 (13)	0	1 (11)
Evolution to normal	6 (40)	7 (64)	4 (44)

Table VI. Clinical Details of Mixed Type

No	Present age /sex	Age at first seizure	Age at last seizure	Family history	Seizure time	Imp cons	Vacant spell	Major seizure type	FS	SE	No AED	Seizure-free	Major EEG finding and evolution	Follow-up (yr)
1	8/F	4	5	FS	N	√	√	V,visual, headache	>10	-	-	√	rt O spikes → normalized	3
2	11/F	6	9.5	-	D	√	√	V, headache	2-5	-	-	√	rt O spikes → normalized	5
3	16.5/F	11	15	-	N	√	√	V, headache, eye deviation	2-5	√	-	√	rt O spikes → and extra O	6
4	11/F	7.5	9	E	D	√	√	V, visual, eye deviation	2-5	-	√	√	N	3
5	16/M	8	16	E	Both	√	√	V, visual, eye deviation	>10	√	-	-	lt O→ lt extra O+ SGD	6
6	15/M	6	10	FS	D	√	√	V, headache	2-5	-	-	√	b O → CSWS → normalized	12
7	12.5/M	8.5	9.5	-	D	√	√	V, visual, eye deviation	2-5	-	-	√	lt O and extra O → lt O + extra O+ SGD	4
8	20.5/F	10	11	-	D	√	√	V, visual, eye deviation	2-5	-	√	√	bO → normalized	10
9	13/F	5.5	6.5	FS/E/M	N	√	√	V, visual, eye deviation	1	-	√	√	bO → bO + SGD	8

AED: Antiepileptic drug, b: Bilateral, CSWS: Continuous spikes and waves during slow sleep, D: Diurnal, Imp Cons: Impairment of consciousness, E: Epilepsy, FS: Febrile seizure, , lt: Left, M: Migraine, N: Nocturnal, O: Occipital, rt: Right, SGD: Secondary generalized discharges, SE: Status epilepticus,V: Vomiting.

(duration from first to last seizure) in the PS type was clearly shorter than in the G-CEOP and the mixed type. The average duration of epilepsy for patients with remission was 40.6 ± 21.2 months (range: 6-120 months). All the patients were evaluated longitudinally, clinically and with EEGs for 2 to 12 years (mean: 5.53 ± 0.43). Psychomotor development was normal in all patients.

e. Atypical evaluation

It is interesting to note that three of our patients had seizures that were initially consistent with Panayiotopoulos type and then progressed to seizures typical of G- CEOP in a long follow-up lasting for 5-7 years, which occurred at the age of the first seizure 1.5 to 3.5 years. Another interesting note is that we observed a girl who initially suffered from clinical and EEG features of childhood absence epilepsy (CAE), which were suppressed with valproic acid, and subsequently (one year later), she presented PS accompanied by interictal EEG findings of bilateral occipital spike-wave paroxysms. In addition, one patient with mixed type (Patient 6, Table VI) demonstrated almost continuous spike-and-wave during sleep (CSWS) at some time during the clinical course. At his last examination, at 15 years of age, he presented mild cognitive impairment although he had been seizure-free for three years.

Discussion

We report a series of 35 well-documented patients who started with early- and late- onset CEOP, with typical or atypical clinical and EEG features. There is a significant variation in the inclusion and exclusion criteria of the two syndromes among the various published reports.[8-12] Some studies have investigated differences in ictal semiology as a means of distinguishing between PS and G-CEOP.[15, 17] Regarding CEOP, this study also confirms that PS is more frequent and benign than G-CEOP.[5, 18-20] The most common ictal symptom in our patients was vacant spells (91%), and it was also the most common ictal symptom in all subtypes of CEOP (93%, 82%, and 100%, respectively; Table III). So far, this has been reported very rarely in patients with idiopathic, usually symptomatic occipital lobe epilepsy has been observed[20-22, 25, 30, 37]. This may be because parents cannot easily overlook vacant spells. Complex partial seizures of presumed temporal lobe origin are reported to begin with eye-moving sensations and similar vacant spell[21-23]. However, the most common spread of seizure of occipital epileptic discharges is infrasylvian, with involvement of the ipsilateral temporal region, and the clinical seizure manifestation would reflect these various spread patterns, such as vacant spell, automatisms or eye blinking[24]. The other common ictal symptoms in the subtypes of CEOP were eye deviation (87%, 45%, 67%, respectively; Table III) and autonomic disturbances (80%, 27%, 78%, respectively; Table III). In the subtypes of CEOP, however, eye deviations with or without head deviation were more common in the PS group than in the GS and mixed groups (87%, 45%, 67%, respectively; Table III), which was the characteristic seizure type in our patients with PS, similar to previous reports[24,25].

Impairment of consciousness, eye deviations with or without head deviation, vomiting, and autonomic disturbances were more common in the PS group than in the G- CEOP, similar to previous reports.[5, 9, 15] Ictal vomiting is likely to be more common in PS, but it was found to be a more common symptom in the mixed type than in the PS, though not statistically significant (Table II).

Visual hallucinations are the most typical and usually the first ictal symptom, and are probably present in more than two-thirds of patients with G-CEOP.[5, 15, 18] Our study also revealed only a slightly lower incidence of visual symptoms in G-CEOP (Table II). However, 41% of our patients were ≤4 years of age at the onset of seizures (notably, 36% of our patients with G-CEOP), and visual symptoms in this younger age group may go unnoticed. It has been reported that the most common ictal visual symptoms in G-CEOP were negative visual symptoms.[9, 15, 16, 26, 27] In this sudy, 36% of patients with G-CEOP had ictal blindness as an initial manifestation of their seizures, similar to the report by van den Hout et al.[20]

Other occipital manifestations more commonly seen in our patients included automatisms and autonomic and ictal behavioral disturbances, as reported previously.[5, 8, 15] Autonomic disturbances alone or together with ictal behavioral disturbances appear as among the most frequent symptoms in PS.[7, 18, 28, 29] If a

seizure spreads to the medial temporal lobe, automatism and impairment of consciousness can occur. Automatisms indistinguishable from those of patients with temporal lobe epilepsy have been reported in 29-88% of patients with occipital lobe epilepsy.[21] In our study, there was only a slightly higher incidence of automatism in PS (40%) than reported previously.[15, 18, 25, 30] These symptoms usually occur in the early stages of seizure. They may be missed in nocturnal seizures.[21] In our study, secondarily generalized tonic-clonic seizure (2GTCs) was found to be a more common symptom in the PS and mixed-type than in the G-CEOP (Table IV). Four patients with PS had experienced 2GTCs at different times, indicating that multiple pathways of spread can be present in a single patient.[31]

EEG is an important tool in the diagnosis and follow-up of patients with CEOP. Abnormalities on EEG are more likely to be detected with multiple recordings and when a sleep study is obtained. This study demonstrated that occipital spikes and occipital paroxysms are an age-related EEG abnormality that may occur in seizure with atypical and/or typical ictal manifestations. The EEG spikes and seizures usually disappear simultaneously or with AED.[3, 15] This study also documents that epileptic discharges disappeared more often in G- CEOP than in the other subtypes, but the difference was not statistically significant (Table IV). Regarding the EEG findings, we showed variable evolutional changes in EEG foci with age, which may have weakened the specificity of CEOP.[15, 30] Patients in whom seizures were active despite normal EEG recordings emphasize the poor correlation between clinical and EEG features in idiopathic epilepsies.[15, 32] We also found that occipital epileptiform discharges had migrated or changed only in patients with PS and mixed type, as reported previously.[11, 16, 33] However, we found a lower incidence of extra-occipital epileptiform discharges in PS, as reported previously,[15] and a slightly higher incidence of migration of epileptiform discharges in the mixed type. As the EEG spike focus itself tends to shift with age regardless of etiology in childhood idiopathic epilepsy,[19, 34, 35] the characteristic spike localization in these two syndromes is reasonably explained by the age window (i.e., occipital spike foci in early childhood, only occipital foci in later childhood, and both during the intermediate period).[8-12, 36] We did not consider EEG abnormalities and localization as essential inclusion or exclusion criteria to comply with current evidence that PS is mainly a multifocal epileptic syndrome with significant EEG variability and typical and/or atypical ictal semiological features. We firstly excluded patients with symptomatic epilepsy and patients with nonepileptic paroxysmal autonomic manifestations only.

Despite the heterogeneity of the CEOP data in the literature reviewed, it seems to result from an evolution of the same maturational process by aging, which also involves rolandic epilepsy and CAE. Atypical evolutions have been reported previously in patients with PS or G-CEOP.[11-13, 17, 22, 37-43] It is interesting to note that three of our patients with PS had progressed to G-CEOP over time, as reported previously. [42] It has been suggested that the neurobiological spectrum of CEOP results in PS semiology early in childhood, and as the brain matures, the features of G-CEOP become more evident.[16] We observed a girl who suffered from CAE and progressed to PS. Similarly, Gambardella et al.[37] firstly reported a boy who experienced PS four years after recovering from an electroclinical picture characteristic of CAE. Additionally, one patient with mixed type had developed electroclinical features similar to the cases described by Caraballo et al.[12] as atypical evolution and epilepsy with CSWS. In the better known overlap of benign rolandic epilepsy and idiopathic generalized epilepsy, there were observations of both syndromes in one family and of both EEG traits in single individuals.[11, 14, 22, 37, 44, 45] None of our patients had developed rolandic epilepsy during the follow-up.

Some studies have focused on atypical clinical features and outcomes in patients with CEOP type.[9, 11, 14, 16, 33, 37, 39-43] They have reported that 28%-50% of their patients presented atypical clinical manifestations of CEOP. These studies also describe those the patients with accompanying atypical clinical features, which make it difficult to comply with the rigidly segregated syndromes reported by several authorities.[10, 11, 39, 40, 41] The report of Taylor et al.[16] emphasized that the overlap of ictal symptoms occurs in both smaller and older children. Kivity et al.[9] reported a large series

of 134 children with ICOE; only 96 (72%) of them could be segregated into either of the rigidly delineated epileptic subtypes. An additional 38 (28%) children failed to comply with either rigid syndrome and had mixed clinical phenomena at various ages of onset. Genizi et al.[8] described a series of 28 children with CEOP, and 14 patients (50%) had mixed clinical manifestations. CEOP shows that the syndromes described by Panayiotopoulos and Gastaut are less distinct than previously thought, with overlap quite common.

Twenty-six percent of our patients had atypical clinical presentations as the initial ictal semiology. For this reason, we described nine patients (26%) who presented a "mixed'' syndrome with features of classical PS and G-CEOP and examined them in detail (as shown in Table 5). The age of onset seizure in the nine children was 2 to 11 years. All patients with mixed type were right-handed. Patients presented combinations of vomiting (100%) along with visual symptoms (66%) and/or eye deviation (66%) and headaches (44%). This finding is in keeping with previous reports.[11, 12, 14, 39, 40-42] Our mixed group had a symptom overlap; this included five patients with eye and/or head deviation that accompanied and followed visual hallucinations. This finding is in contrast with the study of Ferrie et al.[38] in which visual symptoms were not reported during eye and head deviation in the overlapping cases, but is in parallel with cases reported by Kivity et al.[9] and Taylor et al.[16] For example, seizures were characterized by ictal vomiting, adversive manifestations and visual hallucinations, yet were frequent and diurnal (Patient 4). Interestingly, we found that all mixed patients had vomiting, and the incidence of visual symptoms was higher in the mixed group, at a rate of 67%. Furthermore, what is certain is that vomiting in autonomic seizures of PS is different from the ictal vomiting in adults, which is associated with ictal discharges in the temporal lobe of mainly the nondominant hemisphere.[46] It also differs from the ictal vomiting of occipital lobe epilepsy, which occurs after visual symptoms from spread to the nondominant temporal lobe regions.[26, 47]

We found that patients with PS became seizure-free with a clearly shorter active disease duration (duration from the first to last seizure) than in the G-CEOP and the mixed type, as reported previously.[5, 8, 33, 43] In terms of achieving control, the mixed and PS syndromes in our study were easier to control than the G-CEOP, and required two AEDs, yet their long-term prognosis was still good, as reported previously.[6, 7, 28] The mixed group may be better viewed as a continuum, as previous authors have suggested.[3, 28]

Atypical cases are not unique to PS. They occur in all epilepsy syndromes that have heterogeneous clinical characteristics, except for the same onset age, and appear to be nosologically different epileptic syndromes and constitute an age-dependent idiopathic focal epilepsy developing successively with age.[19, 37, 48, 49] They should stimulate further study regarding questions such as the interaction between genetic, epigenetic and acquired causes and the role of "epilesy genes" in causing markedly different phenotypes. Cumulative results indicate a high prevalance of febrile seizure and/or family history of seizure in previous reports and in our study (13%-40%, Table II), indicating that genetic predisposition plays a major role in these syndromes.[5, 16, 19, 36, 39] Our study was not designed for genetic purposes. According to Taylor et al.[16] PS, like rolandic epilepsy, is probably genetically determined, but conventional genetic influences may be less important than other mechanisms. SCN1A mutations have been reported recently in a child [41] and two siblings.[50]

The mechanisms underlying the phenomenon of atypical evolution are not yet well understood. The immature nervous system has a tendency to develop mixed atypical evolution, which can be induced by an epileptic focus during the age-related hypersynchronizing function. This was designated as "hereditary impairment of brain maturation" by Doose and Baier.[44] In patients in the mixed group, we described that the age of seizure onset, presence of atypical ictal manifestations, prolonged seizures, and multiple foci in EEGs demonstrate a clear overlap of PS and G-CEOP characteristics. Thus, typical or atypical ictal and other autonomic manifestations in PS may be attributed to a maturation-related susceptibility of the central autonomic network.[47] These findings appear to support the view that the autonomic clinical

manifestations of PS are likely to be generated by variable and widely spread epileptogenic foci acting on a (temporarily for children) hyperexcitable central autonomic network.[2, 8]

There appear to be ever-increasing reports of "atypical" cases of PS. This issue has been addressed recently by Capovilla et al.[37] and Ferrie et al.[51] However, there are still many issues that require further research and enquiry including diagnostic, epigenetic, genetic, pathophysiological, epidemiological, and management issues. We think that detailed evaluations should be performed to ascertain why some patients apply atypical findings and whether each patient has age-related evolution.

This study has several methodological limitations. As most of the studies including ours were retrospective and as the numbers of patients was limited, further prospective studies are necessary to determine the exact prerequisite criteria for determining the borders of this epileptic syndrome and for clarifying the clinical spectrum within this syndrome. Therefore, further studies are required to assess the many atypical cases, and a careful investigation about detailed seizure semiology is required by video-EEG recording or video-seizure recording to confirm our findings.

In conclusion, the reported accumulated clinical data of children with suspected atypical cases, including our experience, have been discussed herein. The data indicate that a strict delineation into either PS or G-CEOP is not feasible in a high proportion of diagnosed children, even as high as 50% in previous studies. Therefore, the dictate for strict delineation into either the early-onset or late-onset forms of CEOP should be discarded because many children will present mixed clinical findings at various ages.[8, 10, 11, 16, 33, 39, 41] Our observations are in keeping with previous studies, which have shown that substantial variable presentations preclude the delineation of a single unique accredited CEOP.

REFERENCES

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010; 51: 676-685.
2. Engel J Jr. ILAE classification of epilepsy syndromes. Epilepsy Res 2006; 70S: S5-10.
3. Ferrie C, Caraballo R, Covanis A, et al. Panayiotopoulos syndrome: a consensus view. Dev Med Child Neurol 2007; 48: 236-240.
4. Covanis A, Ferrie CD, Koutroumanidis M, Oguni H, Panayiotopoulos K. Panayiotopoulos syndrome and Gastaut type idiopathic childhood occipital epilepsy. In: Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P. Epileptic syndromes in infancy, childhood and adolescence. Montrouge: John Libbey Eurotext; 2005: 227-254.
5. Panayiotopoulos CP. Benign childhood focal seizures and related epileptic syndromes. In: Panayiotopoulos CP. A Clinical Quide to Epileptic Syndromes and their Treatments. London: Springer Healthcare Ltd; 2010: 339-376.
6. Gastaut H. A new type of epilepsy: benign partial epilepsy of childhood with occipital spikes –waves. Clin Electroencephalogr 1982; 13: 13-22.
7. Panayiotopoulos CP. The birth and evolution of the concept of Panayiotopoulos syndrome. Epilepsia 2007; 48:1041-1043.
8. Genizi J, Zelnik N, Ravid S, Shahar E. Childhood epilepsy with occipital paroxysms: difficulties in distinct segregation into either the early-onset or late-onset epilepsy subtypes. J Child Neurol 2007; 22: 588-592.
9. Kivity S, Ephraim T, Weitz R, Tamir A. Childhood epilepsy with occipital paroxysms: clinical variants in 134 patients. Epilepsia 2000; 41: 1522-1533.
10. Covanis A. Correspondence on "Childhood epilepsy with occipital paroxysms: difficulties in distinct segregation into either the early-onset or late-onset epilepsy subtypes" J Child Neurol 2008; 23: 1085-1086.
11. Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable? Epilepsia 2000 ;41**:** 380-390.
12. Caraballo RH, Astorino F, Cersósimo R, Soprano AM, Fejerman N. Atypical evolution in childhood epilepsy with occipital paroxysms (Panayiotopoulos type). Epileptic Disord 2001; 3: 157-162.
13. Ferrie CD, Koutroumanidis M, Rowlinson S, Sanders S, Panayiotopoulos CP. Atypical evolution of Panayiotopoulos syndrome: a case report. Epileptic Disord 2002; 4: 35-42.
14. Caraballo RH, Cersósimo RO, Fejerman N. Late-onset, "Gastaut type", childhood occipital epilepsy: an unusual evolution. Epileptic Disord 2005; 7: 341-346.
15. Ferrie CD, Nordli DR Jr, Panayiotopoulos CP. Benign focal epilepsies of childhood. In: Pellock JM, Bourgeois BFD, Dodson WE, editors. Pediatric Epilepsy: Diagnosis and treatment. 3rd ed. New York: Demos Medical Publishing; 2008: 335-350.
16. Taylor I, Berkovic SF, Kivity S, Scheffer IE. Benign occipital epilepsies of childhood: clinical features and genetics. Brain 2008; 131: 2287-2294.
17. Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain 2008; 131: 2264-2286.

18. Terasaki T, Yamatogi Y, Ohtahara S. Electroclinical delineation of occipital lobe epilepsy in childhood. In: Andermann F, Lugaresi E, editors. Migraine and Epilepsy. Boston: Butterworth; 1987: 125-137.
19. Oguni H, Hayashi K, Imai K, Hirano Y, Mutoh A, Osawa M. Study on the early-onset variant of benign childhood epilepsy with occipital paroxysms, otherwise described as early-onset benign occipital seizure susceptibility syndrome. Epilepsia 1999; 10: 1020-1030.
20. Van den Hout BM, Van der Meij W, Wieneke GH, Van Huffelen AC, Van Nieuwenhuizen O. Seizure semiology of occipital lobe epilepsy in children. Epilepsia 1997; 38: 1188-1191.
21. Holtzman RN. Sensations of ocular movement in seizures originating in occipital lobe. Neurology 1977; 27: 554-556.
22. Caraballo RH, Sologuestua A, Grañana N, et al. Idiopathic occipital and absence epilepsies appearing in the same children. Pediatr Neurol 2004; 30: 24-28.
23. Salanova V, Andermann F, Olivier A, Rasmussen T, Quesney LF. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991. Surgery of occipital lobe epilepsy. Brain 1992; 115: 1655-1680.
24. Ludwig BI, Marsan CA. Clinical ictal patterns in epileptic patients with occipital electroencephalographic foci. Neurology 1975; 25: 463-471.
25. Panayiotopoulos CP. Benign childhood epileptic syndromes with occipital spikes: new classification proposed by the International League Against Epilepsy. J Child Neurol 2000; 5: 548-552.
26. Guerrini R, Ferrari AR, Battaglia A, Salvadori P, Bonanni P. Occipitotemporal seizures with ictus emeticus induced by intermittent photic stimulation. Neurology 1994; 44: 253-259.
27. Caraballo RH, Cersósimo RO, Fejerman N. Childhood occipital epilepsy of Gastaut: a study of 33 patients. Epilepsia 2008; 49: 288-297.
28. Caraballo RH, Cersósimo RO, Fejerman N. Panayiotopoulos syndrome: a prospective study of 192 patients. Epilepsia 2007; 48: 1054-1061.
29. Covanis A. Panayiotopoulos syndrome: a benign childhood autonomic epilepsy frequently imitating encephalitis, syncope, migraine, sleep disorder, or gastroenteritis. Pediatrics 2006; 118: 1237-1243.
30. Taylor I, Scheffer IE, Berkovic SF. Occipital epilepsies: identification of specific and newly recognized syndromes. Brain 2003; 126: 753-769.
31. Takeda A, Bancaud J, Talairach J, Bonis A, Bordas-Ferrer M. Concerning epileptic attacks of occipital origin. Electroencephalogr Clin Neurophysiol 1970; 28: 647-648.
32. Mennink S, van Nieuwenhuizen O, Jennekens-Schinkel A, van der Schouw YT, van der Meij W, van Huffelen AC. Early prediction of seizure remission in children with occipital lobe epilepsy. Eur J Paediatr Neurol 2003; 7: 161-165.
33. Tsai ML, Lo HY, Chaou WT. Clinical and electroencephalographic findings in early and late onset benign childhood epilepsy with occipital paroxysms. Brain Dev 2001; 23: 401-405.
34. Capovilla G, Striano P, Beccaria F. Changes in Panayiotopoulos syndrome over time. Epilepsia 2009; 50: 45-48.
35. Thomas P, Arzimanoglou A, Aicardi J. Benign idiopathic occipital epilepsy: report of a case of the late (Gastaut) type [corrected]. Epileptic Disord 2003; 5: 57-59.
36. Specchio N, Trivisano M, Di Ciommo V, et al. Panayiotopoulos syndrome: a clinical, EEG, and neuropsychological study of 93 consecutive patients. Epilepsia 2010; 51: 2098-2107.
37. Gambardella A, Aguglia U, Guerrini R, Morelli F, Zappia M, Quattrone A. Sequential occurrence of benign partial epilepsy and childhood absence epilepsy in three patients. Brain Dev 1996; 18: 212-215.
38. Ferrie CD, Beaumanoir A, Guerrini R, et al. Early-onset benign occipital seizure susceptibility syndrome. Epilepsia 1997; 38: 285-293.
39. Lada C, Skiadas K, Theodorou V, Loli N, Covanis A. A study of 43 patients with panayiotopoulos syndrome, a common and benign childhood seizure susceptibility. Epilepsia 2003; 44: 81-88.
40. Saitoh M, Kubota M, Kimura I, Mizuguchi M, Igarashi T. A case of Panayiotopoulos syndrome showing an atypical course. Seizure 2006; 15: 643-648.
41. Grosso S, Orrico A, Galli L, Di Bartolo R, Sorrentino V, Balestri P. SCN1A mutation associated with atypical Panayiotopoulos syndrome. Neurology 2007; 69: 609-611.
42. Schrader D, Shukla R, Gatrill R, Farrell K, Connolly M. Epilepsy with occipital features in children: factors predicting seizure outcome and neuroimaging abnormalities. Eur J Paediatr Neurol 2010; 15: 15-20.
43. Wakamoto H, Nagao H, Fukuda M, et al. Idiopathic childhood occipital epilepsy of Gastaut: report of 12 patients. Pediatr Neurol 2011; 44: 183-186.
44. Doose H, Baier WK. Benign partial epilepsy and related conditions: multifactorial pathogenesis with hereditary impairment of brain maturation. Eur J Pediatr 1989; 149: 152-158.
45. Verrotti A, Coppola G, D'Egidio C, Parisi P, Chiarelli F. Gastaut type-idiopathic childhood occipital epilepsy and childhood absence epilepsy: a clinically significant association? Seizure 2010; 19: 368-372.
46. Koutroumanidis M. Ictal vomiting in association with left temporal lobe seizures in a left hemisphere language-dominant patient. Epilepsia 2003; 44: 1259.
47. Panayiotopoulos CP. Autonomic seizures and autonomic status epilepticus peculiar to childhood: diagnosis and management. Epilepsy Behav. 2004; 5: 286-295.
48. Ueno M, Oguni H, Yasuda K, Osawa M. Neurophysiological study of secondary synchronous occipito-frontopolar spikes in childhood. Clin Neurophysiol 2001; 112: 2106-2112.

49. Fejerman N, Caraballo R, Tenembaum SN. Atypical evolutions of benign localization-related epilepsies in children: are they predictable? Epilepsia 2000; 41: 380-390.

50. Livingston JH, Cross JH, Mclellan A, Birch R, Zuberi SM. A novel inherited mutation in the voltage sensor region of SCN1A is associated with Panayiotopoulos syndrome in siblings and generalized epilepsy with febrile seizures plus. J Child Neurol 2009; 24: 503-508.

51. Ferrie CD, Livingston JH. Panayiotopoulos syndrome: learning lessons from atypical cases. Epileptic Disord 2010; 12: 92-94.