소아 특발성 후두엽 뇌전증: 임상적 특징 및 예후인자

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Childhood Idiopathic Occipital Lobe Epilepsy: Clinical Characteristics and Prognostic Factors

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Purpose: Among syndromes of idiopathic occipital lobe epilepsy there are Panayiotopoulos syndrome (PS) and idiopathic childhood occipital epilepsy of Gastaut (ICOE-G). However, the classification of epilepsy syndrome is difficult to diagnose at the first seizure because of varying characteristics. We analyzed the different clinical characteristics and prognostic factors of idiopathic occipital lobe epilepsy.

Methods: Forty-three patients who had at least two unprovoked seizures, no abnormalities on magnetic resonance imaging, no known etiology of seizure, and mainly occipital spikes on electroencephalography were retrospectively enrolled at the Korea University Medical Center. A good prognosis was defined as being seizure-free and taking two or less drugs for 1 year.

Results: Among all patients, the proportion of PS was 44.2%, ICOE-G was 7.0% and unclassified group was 48.8%. The age at seizure onset was 4.5 ± 2.6 years (mean $\pm$ SD) in the PS group, and 8.3 ± 2.1 years in the ICOE-G group. The follow-up duration was 10.8 ± 6.0 years. The percentage that the initial diagnosis had not been changed was 66.7% in the PS group and 100% in the ICOE-G group. Among other related symptoms only emesis ($P < 0.001$) and visual symptoms ($P = 0.007$) had varying characteristics between the PS and ICOE-G groups. Patients with PS had a better prognosis than those with ICOE-G or unclassified group (odds ratio [OR] = 58.8). Patients with 1 more autonomic symptoms had a worse prognosis (OR = 3.8).

Conclusion: This study showed that only symptoms of emesis and visual symptoms can differentiate between PS and ICOE-G. More autonomic symptoms were associated with worse prognosis in childhood occipital lobe epilepsy.

Key Words: Idiopathic occipital epilepsy, Prognosis, Panayiotopoulos syndrome

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Introduction

Idiopathic occipital epilepsies are less common than benign rolandic epilepsy, and account for 20–30% of benign childhood focal epilepsies¹⁾. Because no designed controlled epidemiological studies are available, the precise prevalence of subgroups of idiopathic occipital lobe epilepsy is unknown. In a study by Jung-Chieh Du et al²⁾, the prevalences of each occipital lobe epilepsy subgroup were observed as follows: 25.5% for Panayiotopoulos syndrome (PS), 9.3% for idiopathic childhood occipital epilepsy of Gastaut (ICOE-G), and 65.1% for symptomatic occipital epilepsy (SOE). According to Kang et al³⁾, the prevalence of PS

was 13%, ICOE-G 18%, cryptogenic occipital epilepsy 24%, and SOE 22%.

PS is defined as “age-related focal seizure disorder occurring in early and mid-childhood. It is characterized by seizures, often prolonged, with predominantly autonomic symptoms, and multiple foci on electroencephalography (EEG), often with occipital predominance⁴⁾”. PS is generally benign, but some children continue to have seizures that may be resistant to treatment^{1,5)}. ICOE-G occurring in mid and late-childhood is characterized by brief seizures with visual symptoms, and occipital predominance on EEG^{6,7)}. The prognosis of ICOE-G is unclear, and remission occurs in 50–60% of cases¹⁾. However, visual hallucinations may follow the autonomic manifestation in PS, and ictal vomiting may occur in the progression of seizures in ICOE-G⁸⁾. Both autonomic symptoms and visual symptoms can be seen in both syndromes, but symptoms occur at different times in seizure evolution⁸⁾. Therefore, diagnosing with only a single symptom can cause errors. In fact, only two agreements between three pediatric neurologists were seen in classifying childhood epilepsy with occipital paroxysms⁹⁾. According to a study of R.Gaggero et al., 32.8% of the PS, ICOE-G, and unclassified groups in childhood focal idiopathic epilepsy had their final diagnosis changed by new clinical events or new diagnostic data¹⁰⁾. These changes may be interpreted as a reflection of the natural history of epilepsies rather than a mistake at the first diagnosis.

Classifying the epileptic syndrome at the first episode is difficult and confusing because of its various characteristics. In fact, the final diagnosis of epilepsy syndrome was reassigned in 18% of the first diagnosis in the study of Shinner et al. and 10–12% in the study of Berg et al^{11,12)}. Moreover, PS is one of the most misdiagnosed epilepsy types because autonomic symptoms can be misdiagnosed as migraine, gastroenteritis, syncope, or sleep disorder¹³⁾. In addition, the incidence of atypical PS is increasing, and 10% of the patients undergoing a single routine EEG show unremarkable results, which makes diagnosis difficult. Early accurate diagnosis is important because it provides people with prompt information on appropriate treatment, support and risk reduction. Early classification is also important because some ICOE-G patients show more prolonged non-remitting course than PS with good prognosis.

These considerations prompted this study, which evaluates the possibility of early syndrome classification of idiopathic occipital epilepsy in children at the first seizure and compares the clinical characteristics between PS and ICOE-G. Both PS and ICOE-G have been termed benign epilepsies⁶⁾, but there are patients with poor prognosis. Therefore, we studied the prognostic factors and the possibility of diagnostic confusion in patients with poor

prognosis.

Materials and Methods

1. Patients and methods

The participants included 317 children with occipital epileptiform discharges on EEG at Korea University Medical Center between January 2010 and September 2016. This study was approved by the Institutional Review Boards of Korea University's Anam and Guro Hospitals (IRB No : ED16361, KUGH16376).

The following inclusion criteria was applied: at least two afebrile seizures, and only occipital epileptiform discharges on EEG. The minimum follow-up period was 1 year.

Patients were excluded if they had any of the followings: clinical signs and symptoms of other epilepsy syndromes, epileptiform discharges form in another brain area on EEG, evidence of known etiology (structural abnormality on magnetic resonance imaging [MRI], infection, or metabolic disorder), or a history of intellectual disability or developmental delay.

Patients who met the inclusion criteria were divided into the following three groups: a PS group, ICOE-G group, and unclassified group. Because of their ambiguous diagnostic criteria and the large number of patients with extra occipital spikes in the EEG, patients with spikes in the only occipital area were included. Among them, patients with at least one of autonomic symptoms such as nausea, vomiting, pallor, cyanosis, salivation, lethargy, syncope, and urination were diagnosed with PS. Patients with at least one of visual symptoms such as elementary and complex visual hallucinations, visual illusions, blindness, partial visual loss, sensory hallucinations were diagnosed with ICOE-G. If the above two symptoms were not accompanied or if the time sequence of the two symptoms was ambiguous, it was classified as unclassified. Age at the onset of seizures was not considered as a classification criterion.

We assessed sex, age at first seizure, clinical symptoms, clinical diagnosis, and prognosis through review of retrospective medical records or telephone interviews with patients and parents. To evaluate the relationship between these factors and prognosis, a good prognosis was defined as a patient remaining seizure-free for 1 year and taking 2 or less antiepileptic drugs (AED).

2. Statistical analyses

Data were analyzed using SPSS software (version 20; SPSS, Chicago, IL, USA). The Fisher's exact test was used to compare the variables between 3 subgroups in childhood idiopathic occipital lobe epilepsy. Bilinear logistic regression was used to

identify prognostic factors for classified patients with good or poor prognosis. Statistical significance was defined as $P < 0.05$. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

1. Concordance between the initial and final diagnosis

In our study, 43 patients with childhood idiopathic occipital lobe epilepsy were analyzed during a mean follow-up period of 10.8 ± 6.0 years. Patients were categorized into the following 3 groups: the PS group, ICOE-G group, and unclassified group. After the first seizure, 27 patients (62.8%) were diagnosed with PS, 2 patients (4.7%) were diagnosed with ICOE-G, and 14 patients (32.6%) were unclassified.

The diagnosis of these patients changed according to the repeated prominent symptoms and the characteristics of the clinical events. When the autonomic or visual symptoms were ambiguous were accompanied, they were finally diagnosed as unclassified. At the end of the follow-up, the percentage that the initial diagnosis had not been changed was 66.7% in the PS group, 100% in the ICOE-G group, and the 92.9% in unclassified group (Fig. 1). Among the patients with an initial diagnosis of PS, 9 patients had different final diagnoses. One patient who frequently experienced only visual symptoms was changed to ICOE-G, 4 patients who did not have autonomic symptoms and visual symptoms later were then diagnosed as unclassified, and 4 who had both vomiting and visual symptoms later were then diagnosed as unclassified.

Fig. 1. Comparison between the initial and final diagnosis. Each bar represents the percentage (%) of change of the initial diagnosis. PS, Panayiotopoulos syndrome; ICOE-G, idiopathic childhood occipital epilepsy of Gastaut; Auto & Visual, Patients with autonomic symptoms and visual symptoms; Non-auto & Non-visual, Patients without autonomic symptoms and visual symptoms.

Patients who had both symptoms were diagnosed as unclassified due to lack of time sequence or description of autonomic symptoms and visual symptoms at the time of seizure. Two patients with diagnoses of ICOE-G remained unchanged. Among the patients with an initial diagnosis of unclassified, the diagnosis for 1 patient was changed to PS. Thus, 13 patients remained in the unclassified group. The final diagnosis was 19 patients in the PS group, 3 patients in the ICOE-G group, and 21 patients in the unclassified group.

2. Demographic and clinical data

The final diagnosis of 43 patients was 19 (44.2%) in the PS group, 3 (7.0%) in the ICOE-G group, and 21 (48.8%) in the unclassified group. Patient demographics of the 3 groups are summarized in Table 1. The male and female ratios were 8:11, 1:2, and 14:7, in the PS, ICOE-G, and unclassified groups, respectively. The age at seizure onset was 4.5 ± 2.6 years in the PS group, 8.3 ± 2.1 years in the ICOE-G group, and 5.7 ± 4.6 years in the unclassified group. In the PS group, 6 patients (28.6%) had a history of febrile seizure, 4 patients (19%) had a family history of febrile seizure, and 1 patient (4.8%) had a family history of epilepsy. Conversely, in the ICOE-G group, no patient had a history of febrile seizures or family history of febrile seizures; however this difference was not statistically significant. There were no statistically significant differences between the three groups in terms of seizure type, eyeball deviation, seizure on sleep or wakefulness, duration of

Table 1. Demographics Characters of the Subgroups in Childhood Idiopathic Occipital Lobe Epilepsy

Variables	PS (%)	ICOE-G (%)	Unclassified (%)	P-value
Patient number	19 (44.2)	3 (7.0)	21 (48.8)	
Sex (male/female)	8/11	1/2	14/7	
Age of sz onset (yrs)*	4.5 ± 2.6 (1-10)	8.3 ± 2.1 (6-10)	5.7 ± 4.6 (0-15)	0.857
P/Hx of febrile sz	6 (31.6)	0	5 (23.8)	0.657
F/Hx of febrile sz	4 (21.1)	0	9 (42.9)	0.181
F/Hx of epilepsy	1 (5.3)	0	2 (9.5)	1.0
Sz type				
Generalized sz	16 (84.2)	3 (100)	16 (76.2)	0.840
Focal sz	3 (15.8)	2 (66.7)	6 (28.6)	0.140
Eyeball deviation	13 (68.4)	2 (66.7)	14 (66.7)	1.0
Sz on wakefulness	8 (42.1)	2 (66.7)	13 (61.9)	0.448
Sz on sleep	15 (78.9)	2 (66.7)	13 (61.9)	0.523
Duration of sz >5 min	9 (47.4)	1 (33.3)	8 (38.1)	0.890
Duration of sz >30 min	3 (15.8)	1 (33.3)	5 (23.8)	0.613
Number of AED	0.5 ± 0.6	1.3 ± 0.6	1.0 ± 1.1	0.368
Lifetime total sz number	4.5 ± 6.4	5.3 ± 4.0	4.7 ± 4.4	0.100
Good prognosis	17 (89.5)	2 (66.7)	16 (76.2)	0.371

*Mean $\pm$ SD (min-max).

PS, Panayiotopoulos syndrome; ICOE-G, idiopathic childhood occipital epilepsy of Gastaut; AED, antiepileptic drug; F/Hx, family history; min, minute; P/Hx, past history; Sz, seizure.

seizure, number of AED, number of total seizures, and prognosis.

The clinical features of the 3 groups are shown in Table 2. Nausea or vomiting was observed in 17 (89.5%) patients in the PS and visual symptoms were observed in 3 (100%) patients in the ICOE-G group. Nausea or vomiting was observed in 1 (33.3%) patient in the ICOE-G group; visual symptoms were not observed in any patient in the PS group. Nausea or vomiting were also significantly different between the PS and ICOE-G groups (Fisher's exact test, $P<0.001$), and between the PS and unclassified groups (Fisher's exact test, $P<0.001$). Visual symptoms were significantly different between the PS and ICOE-G groups (Fisher's exact test, $P<0.001$), and between the ICOE-G and unclassified groups (Fisher's exact test, $P=0.028$). However, there was no significant difference in symptoms of pallor, cyanosis, salivation, lethargy, syncope, urination, headache, eyeball deviation, and TV- or game-provoked seizure between 3 groups.

3. Prognostic factors in childhood idiopathic occipital lobe epilepsy

Patients were categorized into two groups. The first group included 35 patients (81.4%) who remained seizure-free for 1 year and taking 2 or less antiepileptic drugs (good prognosis). The second group included 8 patients (18.6%) who did not respond well to AED treatment or were treated with more than 2 AEDs (poor prognosis). According to bilinear logistic regression analysis, patients with PS had a better prognosis than those with ICOE-G and unclassified ($P=0.020$, odds ratio [OR]=58.8). The proportion of patients with a good prognosis included 17 patients (89.5%) in the PS group and 18 patients (75%) in the ICOE-G and unclassified groups (Table 3).

Autonomic symptoms were divided into the following five categories: nausea or vomiting, pallor or cyanosis, salivation,

lethargy or syncope, and urination. The number of autonomic symptoms was significantly associated with poor prognosis. A greater number of accompanied autonomic symptoms was associated with a worse prognosis ($P=0.024$, logistic regression test, OR=3.821). Furthermore, each additional symptom worsens the prognosis by 3.8 times. However, variables such as age at onset of seizure, seizure type, visual symptoms, wakefulness or sleeping during seizures, duration of seizures over 30 minutes, interictal epileptic discharges (IEDs) dominance during sleep or wakefulness on EEG, and fixation-off were not significant prognostic factors (Table 3).

Discussion

Idiopathic occipital lobe epilepsy is not easily identified because of the high rate of misdiagnosis, despite its high prevalence. The main reason for misdiagnosis is that emesis and other autonomic manifestations include pallor, mydriasis, hypersalivation, intestinal motility change, and headache frequently imitate motion sickness, encephalitis, syncope, migraine, sleep disorder, or gastroenteritis¹³. In addition, PS can be misclassified as ICOE-G or Rolandic epilepsy due to overlapping clinical features and EEG findings⁸. The reported difficulties in differentiating ICOE-G from PS may arise when emphasis is unduly placed on individual symptoms that may overlap rather than a comprehensive synthetic analysis of their respective electro-clinical characteristics^{8,14}. For these reasons, this study evaluated the possibility of early syndromic classification of idiopathic occipital epilepsy in children experiencing their first seizure. In our study, 10 patients (23.3%) had a different final diagnosis and 21 patients (48.8%) were in the

Table 2. Clinical Characters of the Subgroups in Childhood Idiopathic Occipital Lobe Epilepsy

Variables	PS n (%)	ICOE-G n (%)	Unclassified n (%)	P-value
Patient number	19 (42.9)	3 (6.1)	21 (51.0)	
Autonomic symptoms	19 (100)	1 (33.3)	15 (71.4)	0.005*
Nausea / vomiting	17 (89.5)	1 (33.3)	6 (28.6)	<0.001*
Pallor / cyanosis	4 (21.1)	0 (0)	7 (33.3)	0.477
Salivation	7 (36.8)	1 (33.3)	6 (28.6)	0.879
Lethargy / syncope	10 (52.6)	0 (0)	7 (33.3)	0.178
Urination	3 (15.8)	0 (0)	2 (9.5)	0.764
Headache	5 (26.3)	2 (66.7)	7 (33.3)	0.371
Visual symptoms	0 (0)	3 (100)	5 (23.8)	0.007*
Eyeball deviation	13 (68.4)	2 (66.7)	14 (66.7)	1.0
TV- or game-provoked sz	0 (0)	0 (0)	2 (9.5)	0.558

* $P<0.05$.

PS, Panayiotopoulos syndrome; ICOE-G, idiopathic childhood occipital epilepsy of Gastaut; n, number; sz: seizure.

Table 3. Factors Predicting Poor Prognosis in Childhood Idiopathic Occipital Lobe Epilepsy

Variables	Good prognosis n (%)	Poor prognosis n (%)	P-value	Odds
Patient number	35 (81.4)	8 (18.6)		
Epilepsy syndromes PS / G+U	17 (89.5)/18 (75)	2 (10.5)/6 (25)	0.020 [†]	0.017
Age of at sz onset (yrs)*	5.4±3.9	5.1±3.6	0.080	
Number of autonomic sx*	1.6±1.1	2.0±1.3	0.024 [†]	3.821
Visual symptoms	6 (17.1)	2 (25)	0.080	
Sz on wakefulness	18 (51.4)	5 (62.5)	0.811	
Sz on sleep	23 (65.7)	7 (87.5)	0.083	
Duration of sz >30 min	6 (17.6)	3 (37.5)	0.502	
IEDs dominance during sleep/ wakefulness/no difference [‡]	13 (37.1)/ 19 (54.3)/3 (8.6)	2 (25)/ 6 (75)/0 (0)	0.232	
Fixation-off	4 (11.4)	2 (25)	0.502	

*mean±SD, [†] $P<0.05$. [‡]Patients with no difference in IEDs dominance among sleep or awakening.

PS, Panayiotopoulos syndrome; G+U, ICOE-G and Unclassified group; n, number; sz, seizure; sx, symptoms; IEDs, interictal epileptic discharges.

unclassified group. This suggests that patients with childhood idiopathic occipital lobe epilepsy are difficult to classify and susceptible to misdiagnosis. In this study, the main reason for the difficulty of diagnosis and the high proportion of unclassified groups was due to the inaccurate history and overlap of clinical features. Capovilla and colleagues concluded that many theoretical and practical points, including diagnostic, genetic, and pathophysiologic issues remain unresolved for PS¹⁵⁾. According to Engel, the criteria for syndrome identification continue to be improved; however, more data are needed because ICOE-G is rare with a paucity of recent confirmatory reports¹⁶⁾.

The cardinal features of PS are autonomic symptoms such as nausea and vomiting, while the cardinal features of ICOE-G are visual symptoms such as visual hallucination and blindness. The results of this study showed that there was a significant difference in these two symptoms, but not among other symptoms. In contrast, one patient (33.3%) with ICOE-G had a seizure event with an autonomic symptom. Four patients who were initially diagnosed with PS showed vomiting and recurrent visual symptoms later, but were not diagnosed as PS or ICOE-G at the final diagnosis. According to other studies, visual symptoms may occur in patients with PS and ictal vomiting following visual symptoms may occur in ICOE-G¹⁷⁾. However, in our study, 33.3% of patients in the first diagnosis of PS changed their final diagnosis, but ICOE-G patients remained unchanged. It is believed that visual symptoms are strongly suggestive of ICOE-G. Therefore, in this study, four patients with autonomic symptoms and visual symptoms are more likely to have ICOE-G. In fact, when compared to PS in combination with ICOE-G and unclassified groups (G+U), autonomic symptoms, nausea or vomiting, and visual symptoms were significantly different (Fisher's exact test, $P=0.006$, $P<0.001$, $P=0.006$, respectively). Therefore, prognosis is compared with PS and G+U as shown in Table 3.

Ictal autonomic symptoms are likely to be generated by variable and widely spread epileptogenic foci acting upon a temporarily hyperexcitable central autonomic network in susceptible children^{14,18)}. This means that the more autonomic symptoms appear, the more rapidly they are spread out in a low threshold central autonomic system. Therefore, in this study, it is considered that the more autonomic symptoms, the worse the prognosis. Autonomic neuropathy in temporal lobe epilepsy occurs well because of the abundant connections between the limbic system and the hypothalamus, which is a poor prognosis as compared with idiopathic occipital lobe epilepsy¹⁹⁾. However, occipital epilepsies characterized with focal seizures can be easily confused with other focal epilepsies originating from the temporal or frontal lobes²⁰⁾. Because of different ictal spread patterns of the initial

occipital discharge, some patients may present with various non-occipital ictal manifestations that mimic those originating in other regions of the cortex and even obscure the initial occipital manifestations²¹⁻²³⁾. Therefore, PS with many autonomic symptoms should be questioned as to whether it is pure PS with a bad prognosis or a condition other than PS such as temporal lobe epilepsy or frontal lobe epilepsy. Careful electro-clinical analysis is therefore required to distinguish these conditions.

As a limitation of this study, the PS sample size would be reduced by excluding epileptic discharges from other multiple foci. We excluded all patients with extraoccipital spikes and limited patients with only occipital epileptiform discharges. Therefore, it is considered that the PS sample size would be reduced by excluding a large number of PS patients with multifocal high amplitude and sharp slow wave complexes in the EEG, and this would have increased the rate of unclassified. In addition, the retrospective nature of this study is a significant limitation. Seizure semiology was also only reported by witnesses and clinical characteristics were insufficient.

In conclusion, it was difficult to initially classify idiopathic occipital epilepsy in children; it was also easy to misdiagnose. Emesis or visual symptoms, which are the key symptoms that classify the subgroups, may also be seen in patients in other subgroups. PS had a better prognosis than the ICOE-G or unclassified groups, but patients with more autonomic symptoms had a worse prognosis. PS with a poor prognosis should be carefully examined when considering a diagnosis of extra-occipital epilepsy.

요약

목적: 특발성 후두엽 뇌전증에는 Panayiotopoulos 증후군(PS)과 Gastaut형 특발 소아 후두엽뇌전증(ICOE-G)이 있다. PS는 자율신경 증상이 나타나며 ICOE-G는 시각 증상으로 특징 지어진다. 그러나, 간질 증후군은 증상이 모호하고 다양하여 초기에 진단하기가 어렵다. 따라서 본 연구에서 특발성 후두엽 뇌전증의 초기진단과 최종진단의 일치율을 평가하고 임상 양상과 예후 인자를 분석하였다.

방법: 2회 이상의 비유발성 발작이 발생했고, 자기공명영상에 이상이 없고, 발작의 원인 없이 후두부 발작파를 동반한 43명의 환자를 대상으로 하였다. 첫발작시 진단과 최종진단을 비교하였으며, 경련발작 시작 연령, 임상증상, 예후를 조사하였다. 좋은 예후는 1년 동안 2개 이하의 약물로 발작이 없는 상태로 정의했다.

결과: 총 환자 중 PS군은 44.2%, ICOE-G군은 7.0%, 분류되지 않은 군은 48.8%로 분류되었다. 발작 시작 연령은 PS군은 4.5 ± 2.6 년, ICOE-G군은 8.3 ± 2.1 년이었다. 추적 관찰 기간은 10.8 ± 6.0 년이었다. 초기 진단이 변하지 않은 비율은 PS 군에서 66.7%, ICOE-G군에서 100%였다. 구토($P<0.001$)와 시각 증상($P=0.007$)만이 PS와 ICOE-G

군 사이의 유의한 차이를 보였다. PS군이 ICOE-G 또는 분류되지 않은 군보다 예후가 좋았다(OR=58.8). 동반된 자율신경증상(오심 또는 구토, 창백 또는 청색증, 침 분비, 혼수 또는 실신, 배뇨)의 가짓수가 많을수록 나쁜 예후를 보였다(OR=3.8).

결론: PS군과 ICOE-G군을 진단할 때에 변별 증상으로는 구토 증상과 시각 증상만 유의하게 차이를 보였다. 소아기 후두엽 뇌전증에서 자율신경증상이 많이 동반되는 환자는 나쁜 예후를 예측할 수 있겠다.

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