Original article

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Panayiotopoulos syndrome and symptomatic occipital lobe epilepsy of childhood: a clinical and EEG study

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ABSTRACT – *Aim*. Panayiotopoulos syndrome (PS) is an age-related seizure susceptibility syndrome that affects the central autonomic system. Although the majority of the few ictal recordings obtained so far suggest an occipital origin, semiological and interictal EEG data appear to favour more extensive involvement. In this study, the characteristics (including those based on semiology and EEG) of children with Panayiotopoulos syndrome (*n*=24) and those with lesion-related, symptomatic occipital lobe epilepsy (SOLE) (*n*=23) were compared.

Methods. Detailed semiological information and EEG parameters including the localisation, distribution, density (n/sec), reactivity, and morphological characteristics of spike-wave foci and their relationship with different states of vigilance were compared between the two groups.

Results. The age at seizure onset was significantly younger in patients with symptomatic occipital lobe epilepsy than in those with PS (mean age at onset: 3.4 *versus* 5.6 years, respectively; *p*=0.044). Autonomic seizures (*p*=0.001) and ictal syncope (*p*=0.055) were more frequent in PS than in symptomatic occipital lobe epilepsy (87.5% and 37.5% *versus* 43.5% and 13%, respectively). The interictal spike-wave activity increased significantly during non-rapid eye movement (non-REM) sleep in both groups. The spike waves in non-REM seen in PS tended to spread mainly to central and centro-temporal regions.

Conclusions. The results indicate that although common features do exist, Panayiotopoulos syndrome differs from symptomatic occipital lobe epilepsy and has a unique low epileptogenic threshold related to particular brain circuits.

Key words: Panayiotopoulos syndrome, symptomatic occipital lobe epilepsy, occipital, EEG, semiology

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Panayiotopoulos syndrome (PS) is the second most frequent focal idiopathic epilepsy syndrome of childhood after benign epilepsy of childhood with centro-temporal spikes (BECTS) (Panayiotopoulos, 2005). Although its clinical basis has been discussed in detail in many publications, PS is still a focus of interest for phenomenological considerations. A current topic of interest is the proposal to describe PS as an "age-related seizure susceptibility syndrome", instead of referring to it as "epilepsy" (Panayiotopoulos, 1999; Panayiotopoulos, 2005). The basic argument supporting this novel description is that PS is not specifically an "*early-onset form of idiopathic occipital lobe epilepsy (IOLE), but it is rather an age-related syndrome characterised mainly by autonomic seizures*" (Panayiotopoulos *et al*., 2008; Michael *et al*., 2010). Although occipital interictal spikes predominate on the EEG, multiple localisation is not uncommon (Caraballo *et al*., 2007; Leal *et al*., 2008; Saito *et al*., 2008) and cases of seizures originating from variable cortical regions have been reported (Koutroumanidis *et al*., 2005; Specchio *et al*., 2010).

These considerations prompted this study which compared the clinical and EEG findings in patients with PS and symptomatic occipital lobe epilepsy (SOLE) in order to determine the relationship between PS and occipital dysfunction.

Patients and methods

In this study, 24 PS patients were enrolled who had been followed in our outpatient clinic for at least two years and had a follow-up EEG within the past year. The mean patient age was 7.4 years (range: 3-12 years), and all had normal cranial magnetic resonance imaging (cMRI). The second patient group included 23 patients (mean age: 6.7 years; range: 2.5-13 years) with a diagnosis of SOLE based on the clinical and EEG features and cMRI findings. The SOLE patients were matched by age with the PS group and had lesions localised to the occipital region on cMRI and normal EEG background activity during wakefulness and sleep. Epilepsy was classified according to the International League Against Epilepsy Commission on Classification and Terminology (Berg *et al*., 2010). Detailed personal and family histories, neurological and necessary laboratory examinations, and seizure characteristics were recorded. The most informative EEG recordings during wakefulness and sleep, including at least one sleep cycle of the patients, were analysed by two independent electroencephalographers blinded to the type of epilepsy. The EEG parameters included localisation, distribution, density (n/sec), reactivity, and morphological characteristics of spike-wave (SW) foci, as well as their relationship with different states of vigilance. The density of SW discharges represented the average SW activity per second while awake and during non-REM stages, in each hemisphere.

The statistical tests used to compare the data included the *t*-test, Pearson χ^2 test, Fisher's exact test, Mann-Whitney *U*-test, McNemar test, and Wilcoxon signed-rank test.

Results

Demographics

Boys outnumbered girls in the SOLE group (3.6:1) compared with the PS group (1:1) (p=0.044), and the symptoms began earlier with mean ages at onset of 3.4 *versus* 5.6 years, respectively (p=0.004). The proportion of patients with seizure onset before age 4 was 61% in the SOLE group and 17% in the PS group (*figure 1*).

Aetiology

The neurological and imaging findings of the SOLE patients are summarised in *table 1*. Causal factors appeared to be prenatal in three patients (foetal hypoxia) and perinatal in 14 patients (13 with hypoxic/ischaemic damage and one with encephalitis). Six patients had postnatal involvement: head trauma in 2, encephalitis in 3, and cerebrovascular ischaemia in 1.

Seizure characteristics

As demonstrated in *table 2*, autonomic seizures (p=0.001) and ictal syncope (p=0.055) were significantly more frequent in the PS group compared with the SOLE group. Features such as eye and head deviation and facial motor seizures were more common in PS, albeit without statistical significance. Hemiclonic seizures were more frequent in the SOLE group. In the PS group, 13 patients (54.2%) had seizures only during sleep, while 8 (33%) had seizures mainly during sleep. No remarkable difference in seizures was evident between waking and sleep cycles in the SOLE group.

EEG

The mean age at the time of the EEG recordings was 7.4 years for PS and 6.7 years for SOLE. Reactivity to eye opening and eye closure was similar in both patient groups (85 *versus* 92%, respectively). No significant group difference was observed with regards to reactivity to intermittent photic stimulation or hyperventilation. SW activity with occipital localisation was present in 66.7% (n=16) and 65.2% (n=15) of the PS *versus* SOLE groups, respectively, while awake. There was a marked increase in the frequency of SW activity in each hemisphere during non-REM stages. The results were significant for both groups (PS: right

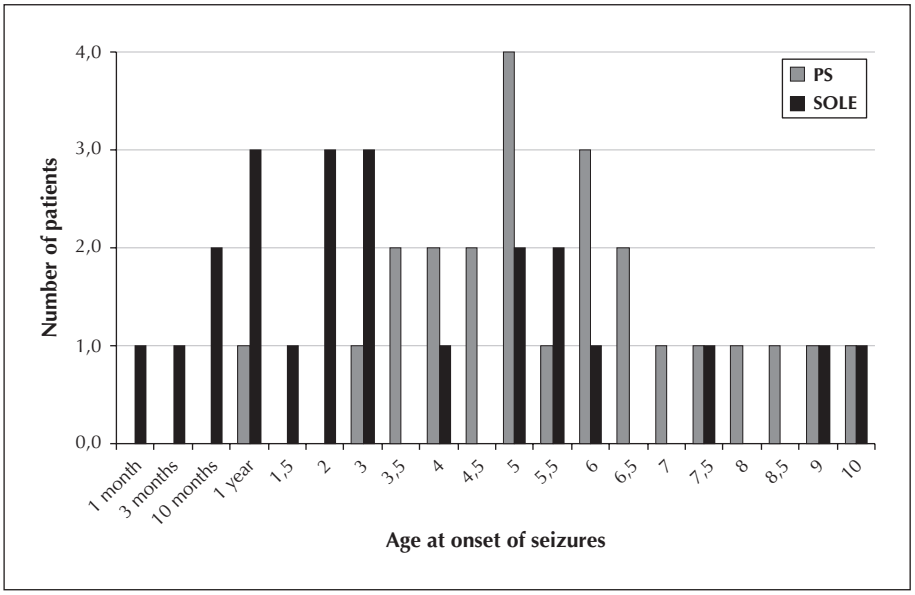

Figure 1. Age distribution of seizure onset in Panayiotopoulos syndrome and Symptomatic Occipital Lobe EPilepsy groups.

occipital SW activity, p=0.005 and left occipital SW activity, p=0.008; SOLE: right occipital SW activity, p=0.004 and left occipital SW activity, p=0.004).

While awake, the occipital SW activity had a tendency to spread in 46% (n=11) of the EEGs, mainly to the central (n=3) and centro-temporal (n=4) areas. The tendency of SW activity to spread was unremarkable in the SOLE group (p=0.01). The data on SW activity spread during non-REM sleep also revealed significant differences between the PS (n=12) and SOLE (n=5) groups (p=0.044).

Extra-occipital SW activity with centro-temporal and central predominance was present in 25% of the PS group while awake and in 38% during non-REM sleep. In the SOLE group, three patients (13%) had extra-occipital SW activity only during non-REM sleep, and all of them showed lateral temporal loci.

Discussion

In this study, we compared the clinical and EEG features of patients with PS and SOLE associated with documented residual structural occipital lobe lesions. As is seen in *figure 1*, the mean age at epilepsy onset in the SOLE group was approximately two years younger than that in the PS group. This was expected, since all patients with SOLE were exposed perinatally to the cause of their epilepsy, at a time of intense vulnerability of the brain to seizures (Velísková *et al*., 2004), and seizures due to moderate or severe cerebral injury related to hypoxic-ischaemic insults start mostly in the early years of life (Robertson and Finer, 1988). On the other hand, PS is firmly age dependant and onset peaks at 3 to 6 years of age (Adcock and Panayiotopoulos, 2012).

Autonomic seizures and ictal syncope were significantly more common in the PS group in our series. Ictal syncope or syncope-like epileptic seizures appear to stand out in the clinical semiology of PS (Koutroumanidis *et al*., 2012). Nearly 90% of the patients in the PS group had autonomic seizures, mainly including ictal nausea, vomiting, retching, pallor, and gastrointestinal disturbances, such as abdominal pain and diarrhoea. One patient had a penile erection as an ictal sign during a video-EEG recording session in our laboratory. Autonomic involvement was reported in less than half of our SOLE patients. Autonomic seizures are described as epileptic seizures characterised by altered autonomic function of any type at seizure onset, or in which manifestations consistent with altered autonomic function are prominent (quantitatively dominant or clinically important), even if not present at seizure onset. The altered autonomic function may be objective, subjective, or both (Ferrie *et al*., 2007). The majority of the autonomic seizures were prolonged in both of our patient groups, but the exact durations were not recorded. The pathophysiological basis of the prolongation of the autonomic seizures is unclear. Perhaps the mutual interaction between the sympathetic and parasympathetic systems, such as between the reciprocal functions of central structures and end-organs, has a competitive effect, which might negatively influence the seizure-terminating mechanisms in autonomic seizures. This is a question for further studies. In our experience, detailed interviews or video recordings of prolonged autonomic

seizures can disclose features suggesting fluctuations in a child's reactivity to environmental stimuli or the severity of autonomic symptoms throughout the seizure. Such prolongation characterised by waxing and waning might be related to the presumed competitive mechanism in autonomic dysregulation. The age-dependent nature of autonomic seizures is well-known and they are more frequent in children than the elderly. The exceptional frequency of autonomic seizures in PS is hypothesised to be due to an age-related, genetically determined low-threshold in the excitability of the autonomic system, independent of the starting point of the seizure activity, which is frequently occipital (Ferrie *et al*., 2007). In the SOLE group, the autonomic seizures might simply be explained in relation to the diffusion of discharges to the temporal regions, which contain the majority of the autonomic centres (Kuzniecky, 1998; Ferrie *et al*., 2007).

Head/eye deviation, as a seizure symptom, was present in 80% and 60% of our patients with PS and SOLE, respectively. Head and eye deviation along with secondary generalisation were the two most frequent

Table 1. Neurological and cranial imaging characteristics of patients with symptomatic occipital lobe epilepsy.

No	Neurological features	Localisation of cranial imaging findings (all residual lesions)
1	Strabismus	cMRI: bi-PO
2	Strabismus; right hemiparesis; MMR	cMRI: left PO; left putamen, insula, caps ext.
3	Right hemiparesis; dysphasia	cCT: left PO
4	Visual loss, MMR	cMRI: bi-PO
5	Left hemiplegia	cCT: right PO
6	Left hemiparesis, MMR	cMRI: right FT; bi-PO
7	Strabismus, left hemiparesis, MMR	cMRI: R>L biPO
8	Strabismus, MMR	cMRI: right O
9	MMR	cMRI: bi-PO
10	Behavioural problems	cMRI: bi-PO
11	Right-sided visual & tactile inattention; behavioural problems; mild MMR	cCT: left PO
12	Vision loss, left hemiparesis, MMR	cMRI: R>L bi-O, right T
13	MMR	cMRI: bi-PO
14	Normal	cMRI: bi-O
15	Behavioural problems, MMR	cMRI: hydrocephalus; cystic lesion in R cerebellar hemisphere
16	Normal	cMRI: bi-PO
17	Strabismus, microcephalus, MMR	cMRI: bi-O
18	Vision loss, MMR	cCT: bi.PO
19	MMR	cMRI: R>L bi-PO
20	Right hemiparesis	cMRI: left FPO
21	Strabismus, MMR	cMRI: bi-O
22	Strabismus, right hemiparesis, MMR	cMRI: bi-PO
23	Strabismus, right hemiparesis, MMR	cMRI: bi-PO

MMR: motor and mental retardation; P: parietal; O: occipital; T: temporal; F: frontal; R: right; L: left.

Table 2. Seizure symptomatology and incidences in PS and symptomatic occipital lobe epilepsy groups.

Seizure symptoms	PS *n* (%)	SOLE *n* (%)
Autonomic seizures**	21 (87.5)	10 (43.5)
Ictal syncope*	9 (37.5)	3 (13)
Head and/ or eye deviation	19 (79.2)	14 (60.9)
Secondary generalisation	13 (54.2)	14 (60.9)
Complex partial symptoms	8 (33.3)	9 (39.1)
Hemiclonic seizure	7 (29.2)	11 (47.8)
Visual seizures	5 (20.8)	5 (21.7)
Oro-facial motor symptoms	5 (20.8)	1 (4.3)
Unilateral eye-blinking	4 (16.7)	5 (21.7)
Motor status epilepticus	8 (33.3)	8 (34.8)

**p=0.001: significant; *p=0.055: near significance.

seizure types in the SOLE group. Seizures with visual involvement were almost equally present in approximately a third of each patient group. Since SOLE clearly has an occipital onset, an abundance of positive or negative visual phenomena should be expected in those patients. However, the incidence of visual symptoms in either group might be under-reported because the experience is subjective and information obtained from a young child may be incomplete.

More than half of the patients in the PS group had seizures only during sleep, and an additional third had seizures mainly during sleep. Seizures occurring only while awake were very rare for both groups. The activating effect of non-REM sleep on spike-wave discharges has been reported (Herman *et al*., 2001; Saltik *et al*., 2005; Loddenkemper *et al*., 2011), and various mechanisms involving anatomically and functionally-related groups of neurons, potentially constituting a network that can initiate and sustain seizure activity, have been proposed (Spencer, 2002).

Interictal SW activity on the EEG was present in nearly two thirds of the patients in both groups while awake and in all patients during sleep. The SW density was markedly higher in non-REM *versus* the awake stage in both the PS and SOLE groups. This was also significant with regards to individual hemispheres. EEG discharges occur during sleep in children with focal idiopathic syndromes, such as BECTS (Nicolai *et al*., 2006) and PS (Panayiotopoulos, 2007). In this study, however, the increase in the SW density during the non-REM period in the SOLE group was prominent and appears to favour similarity between PS and SOLE in terms of the behaviour of the SW activity and different levels of vigilance.

Occipital SW activity in sleep showed a marked tendency to spread in the PS group, compared with the SOLE patients, to the ipsilateral centro-temporal regions. The predominance of centro-temporal SW activity among extra-occipital foci in the PS group and the involvement of the centro-temporal areas by the spreading ipsilateral occipital SW activity might be considered as evidence supporting the concept of PS and BECTS as age-related focal seizure susceptibility syndromes (Caraballo *et al*., 2007). Although PS and BECTS share some common clinical and EEG characteristics, there is also evidence of genetic differences between the two syndromes (Ohtsu *et al*., 2008).

In conclusion, our results concur with studies indicating that PS involves the clinical and EEG expression of age-related dysfunction in the brain circuitry pertaining mainly to autonomic regulation, rather than a localisation-related epileptic syndrome, and suggest that PS has unique features compared with SOLE. Another argument in favour of conceptualising PS as a system-related dysfunction, rather than localisation-related epilepsy, is based on the observation that not all documented seizures have an occipital onset on EEG (Koutroumanidis *et al*., 2005; Specchio *et al*., 2010). In our experience, all of the patients with PS who had an ictal EEG (n=6) during sleep in our laboratory showed repetitive spikes originating from either occipital lead before the onset of any behavioural symptoms. Such a case was reported by Demirbilek and Dervent (2004). The frontal spikes in the EEGs of patients with PS were recently referred to as a secondary activation triggered by occipital discharges, suggesting postero-anterior propagation (Leal *et al*., 2008), and this spread of epileptic activity forms an extended network in PS

(Leal *et al*., 2007; Leal *et al*., 2013). The occipital spikes in PS were also reported to be an age-related phenomenon, as frontal spiking was seen in individuals who were older than those with spikes in the rolandic, parieto-occipital, or calcarine sulci (Saito *et al*., 2008). Although both the seizures and EEG features of PS suggest a unique low epileptogenic threshold involving particular brain circuits with age-dependant vulnerability, there are similarities between PS and SOLE, including the presence of long-lasting autonomic seizures, reactivity, and the sleep-wake characteristics of SW activity on EEG. These could cause diagnostic uncertainty. □

Disclosures.
All the authors certify that there is no conflict of interest with any financial interest.

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