ORIGINAL ARTICLE

PLEDS: Clinical Correlates

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ABSTRACT: ***Objective:*** We reviewed our experience in 96 consecutive patients exhibiting periodic lateralized epileptiform discharges (PLEDs) on EEG. ***Methods:*** EEG reports from January 1, 1999 to September 30, 2006 were screened for the term 'PLEDs' and its variants. A retrospective chart review, including examination of neuroimaging and other investigations, was conducted on each patient identified. ***Results:*** Acute stroke, tumor and central nervous system infection were the most common etiologies, accounting for 26%, 12% and 12% of cases respectively. Acute hemorrhage and traumatic brain injury combined accounted for another 12%. Previously unreported etiologies included posterior reversible encephalopathy syndrome (PRES), familial hemiplegic migraine and cerebral amyloidosis. There were 9 cases of chronic PLEDs attributable to underlying cortical dysplasia or severe remote cerebral injury, all with an accompanying partial seizure disorder. A prominent role for alcohol withdrawal was noted, and in 6 cases was the sole etiological factor. Fever was present as a potential contributing factor in 40% of cases, and significant metabolic abnormalities in 35%. Seizure activity occurred in 85% of patients overall, but in 100% of patients with PLEDs Plus and BiPLEDs Plus. The overall mortality rate was 27%. Mortality among patients with BiPLEDs however was almost twice that, at 52%. ***Conclusions:*** This case series demonstrates the wide variety of potential PLED etiologies. It also emphasizes that despite advances in neurocritical care, the morbidity and mortality associated with PLEDs has changed little since their recognition four decades ago.

RÉSUMÉ: PLEDS : corrélations cliniques. ***Objectif :*** Nous avons revu notre expérience concernant 96 patients consécutifs présentant des décharges épileptiformes latéralisées périodiques (PLEDs) à l'ÉEG. ***Méthodes :*** Nous avons vérifié si le terme « PLEDs » ou ses variantes figurait dans les rapports d'ÉEG émis entre le 1er janvier 1999 et le 30 septembre 2006. Nous avons révisé rétrospectivement les dossiers de tous les patients identifiés et nous avons examiné la neuroimagerie ainsi que les autres examens effectués. ***Résultats :*** Les étiologies les plus communes étaient un accident vasculaire cérébral aigu, une tumeur et une infection du système nerveux central, chez 26%, 12% et 12% des cas respectivement. Un autre 12% était dû soit à une hémorragie aiguë ou à un traumatisme crânien. D'autres étiologies, soit le syndrome de leucoencéphalopathie réversible postérieur, la migraine hémiplégique familiale et l'amyloïdose cérébrale n'ont jamais été rapportées antérieurement. Il y avait 9 cas de PLEDs chroniques attribuables à une dysplasie corticale sous-jacente ou à un traumatisme cérébral ancien sévère et tous ces patients présentaient une épilepsie partielle. On a remarqué que le sevrage alcoolique jouait un rôle important et que c'était le seul facteur étiologique chez 6 patients. La présence d'une hyperthermie était un facteur qui avait pu contribuer chez 40% des patients et des anomalies métaboliques significatives chez 35%. On a observé une activité épileptique chez 85% de tous les patients et chez 100% de ceux chez qui on a observé des PLEDs Plus et des BiPLEDs Plus. Le taux de mortalité global était de 27%. Cependant le taux de mortalité des patients ayant des BiPLEDs était presque le double, soit 52%. ***Conclusions :*** Cette étude démontre la grande variété d'étiologies des PLEDs. De plus, malgré les progrès réalisés dans le domaine des soins neurocritiques, la morbidité et la mortalité associées aux PLEDs ont peu changé depuis leur identification il y a une quarantaine d'années.

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Periodic lateralized epileptiform discharges (PLEDs) are an uncommon electroencephalogram (EEG) pattern characterized by lateralized or focal periodic or near periodic spike, spike-wave, or sharp wave complexes present throughout most or all of the recording. Chatrian introduced the term PLEDs in 1964, though the phenomenon was first described in 1952 by Echlin, Arnett and Zoll.[1] Periodic lateralized epileptiform discharges occur in all age groups, from infants to adults. They are usually seen transiently in the setting of an acute destructive cerebral lesion, and occur early in the course of patient illness.[1-8] They can be seen less commonly with systemic disturbances and a remote cerebral lesion.[7-12] Rare chronic PLEDs, persisting for a period of three months to more than 20 years, have been reported in patients with chronic brain lesions and associated partial seizure disorders.[4,8,12-14] Bilateral, independently occurring PLEDs (BiPLEDs) were recognized by Chatrian[1] in 1964, and formally characterized in 1981 by de la Paz and Brenner.[15] They are seen in the setting of multifocal or diffuse cerebral injury, such as anoxia, and herald a less favorable prognosis with higher mortality.[7,8,15,16]

Approximately 80-90% of patients with PLEDs experience clinical seizure activity, primarily focal motor seizures.[1-8,17-23] In

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1991, Reiher described the entity "PLEDs Plus", characterized by PLEDs admixed with high frequency, low voltage "polyspike" rhythms. These have an even stronger correlation with clinical seizures and status epilepticus.[24] PLEDs are generally not considered an ictal pattern, though this has been reported, and remains a matter of ongoing debate.[25-29]

In this study we reviewed the etiologic factors and clinical correlates in 96 consecutive patients with PLEDs on EEG, with comparison to previously published literature on this subject.

Methods

Electroencephalogram reports from recordings conducted at Royal University Hospital in Saskatoon from Jan 1, 1999 to Sep 30, 2006 were electronically screened for the term 'PLEDs' and its variants. Of the 12,529 outpatient and 3602 inpatient EEGs performed during this time frame, 136 EEGs from 96 patients were identified. Our hospital is the sole neurology tertiary care facility for the northern two-thirds of the province, servicing a population of approximately 500 000 to 750 000. Our electrodiagnostic facility provides the only EEG service for this population. The EEGs were performed on 24-channel Cadwell Easy Writer machines, using the 10-20 international system of electrode placement. The EEGs were performed in emergency room and ICU settings as well as in the electrodiagnostic laboratory. The EEGs were generally performed because of definite or suspected clinical seizure activity, or for investigation of altered level of consciousness. All EEGs were read by a single Canadian certified electroencephalographer. Periodic lateralized epileptiform discharges phenomena were defined as outlined in Table 1. Seizure discharges were distinguished from PLEDs by their evolution in frequency, amplitude and distribution. When multiple EEGs were available on a single patient, PLED evolution was followed in sequential recordings.

Table 1: Definitions of PLED subtypes †

PLEDs	Repetitive, rhythmic lateralized or focal spike, spike-wave, or sharp wave complexes recurring at regular or nearly regular intervals throughout most or all of the EEG recording with return to background activity between discharges, and without clear evolution in frequency or location
PLEDs Plus	PLEDs admixed with rhythmic high frequency, low voltage, polyspike rhythms
BiPLEDs	Bilateral, independently occurring asynchronous PLEDs
BiPLEDs Plus	BiPLEDs with unilateral or bilateral PLEDs Plus
Chronic PLEDs	PLEDs persisting on multiple EEG recordings for a period exceeding three months*

† PLED determination was based on interictal recordings; * Although defined as those persisting for more than three months, as defined by Westmoreland, all patients determined to have chronic PLEDs were found to have persistent PLEDs on both inpatient and non-acute outpatient recordings over a minimum time period of 19 months.

A retrospective chart review, including examination of neuroimaging and other investigations, was conducted on each patient to determine the underlying etiology in each case. The pathology was correlated with PLED subtype and localization. The occurrence and type of associated seizure activity was noted, and mortality data was recorded. Also noted was the presence of significant fever, defined as recurrent or persistent temperature elevation ≥38.5ºC during the 36-48 hour period surrounding the EEG recording. Metabolic abnormalities during this time period were also documented. Significance was determined by the magnitude of the abnormality, and its' recurrence or persistence over time.

Results

Periodic lateralized epileptiform discharges were identified on 136 EEG recordings from 96 patients. This equates with an overall prevalence of 0.8% among all inpatient and outpatient EEG recordings. No patients were excluded. Study group characteristics including patient demographics and a breakdown of PLED subtype are outlined in Table 2. Representative examples of PLEDs, PLEDs Plus and BiPLEDs are illustrated in Figures 1, 2, and 3 respectively. In patients with multiple EEGs, excluding cases of chronic PLEDs, the PLEDs clearly evolved and abated in the usual manner, with decreasing frequency and complexity, over the expected time frame of 2-4 weeks.

Table 2: Study group characteristics

No. Patients		96
Gender (Male : Female)		47 : 49
Patient Age	**Age Range and Mean**	1.5 - 98 years (Mean 61)
	No. Under Age 18	6
Mortality Rate	**Overall**	27%
	BiPLEDs Group	52%
PLED Subtype	**PLEDs**	57 Acute, 6 Chronic
	PLEDs Plus	9 Acute, 3 Chronic
	Right PLEDs/ PLEDs Plus	41 (55%)
	Left PLEDs/ PLEDs Plus	34 (45%)
	BiPLEDs	16 Acute
	BiPLEDs Plus	5 Acute
Seizure Incidence	**Overall**	85%
	PLEDs Plus/ BiPLEDs Plus Groups	100%
	BiPLEDs Group	69%
Seizure Type	**Partial**	74 (90%)
	Focal Motor	63
	Complex Partial †	11
	Generalized	6 (7%)
	Epilepsia Partialis Continua (EPC)	18 (22%)
	Status Epilepticus	23 (28%)
	Nonconvulsive Status Epilepticus	11 (13%)

† Temporal, Frontal or Occipital Types

PLED Etiologies

Table 3 summarizes the primary diagnoses and PLED subtype obtained in the study group. The most common primary etiology

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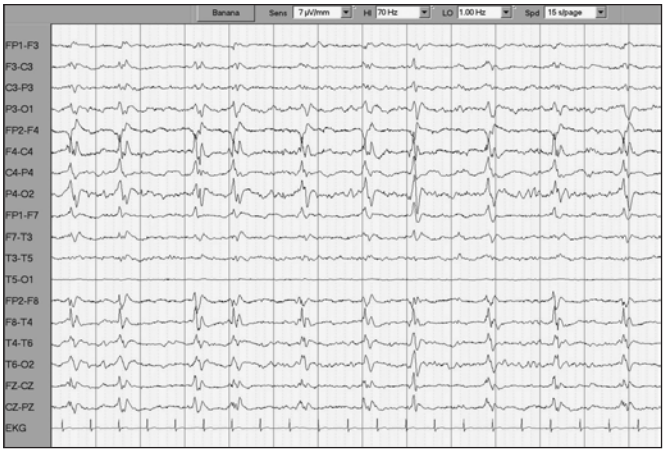

Figure 1: *Right-sided PLEDs in a 77-year-old man with an acute right parieto-temporal hemorrhagic contusion and overlying subdural hematoma.*

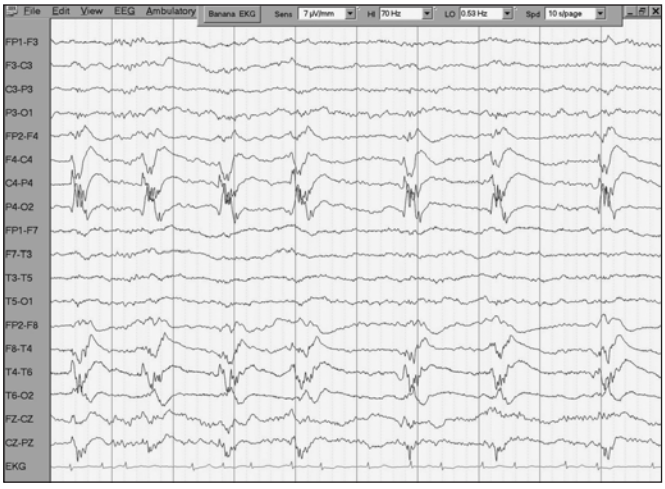

Figure 2: *Right hemisphere PLEDs Plus in an 87-year-old woman with an acute stroke in the right middle cerebral artery territory, and persistent left arm epilepsia partialis continua.*

was acute cerebral infarction, accounting for 25 cases or 26%. Tumor, acute CNS infection, and acute hemorrhage each accounted for 11 cases (12%). Other acute and miscellaneous etiologies are outlined. Etiology was undetermined in one patient with PLEDs and another with BiPLEDs Plus, due to inadequate retrospective data.

Six patients with a strong history of alcohol abuse presented with presumed alcohol withdrawal seizures, five with PLEDs and one with BiPLEDs. No acute or remote focal cerebral pathology could be identified on neuroimaging, though all had marked cerebral and cerebellar atrophy and chronic microvascular subcortical ischemic changes. Cerebrospinal fluid (CSF) analysis and other investigations were normal.

Chronic PLEDs or PLEDs Plus were identified in the three patients with ipsilateral cortical dysplasia and six patients with other remote ipsilateral pathology (Table 3). The patients with cortical dysplasia were aged 11, 13 and 30 years. All had undergone prior epilepsy surgery and had chronic partial seizure disorders. Five of the six patients with other remote pathology and chronic PLEDs had sustained significant cerebral injuries in childhood: tumor resection (n=1), severe traumatic brain injury (n=2), AVM rupture (n=1), and perinatal intracerebral hemorrhage resulting in cerebral palsy (n=1). As adults, each had persistent partial seizure disorders.

Seizure Occurrence and Mortality

Clinical seizure activity was observed in 85% of the study group, including 100% of patients with PLEDs Plus or BiPLEDs Plus (Table 2). Seizure activity occurred within hours to a maximum of 5 days from the time of PLED recording on EEG.

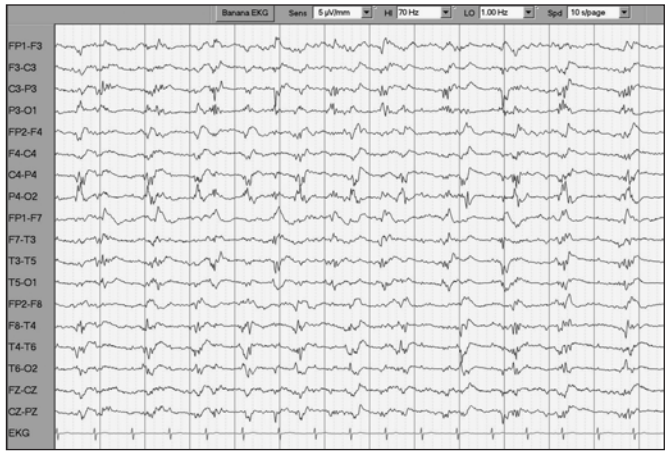

Figure 3: *Bilateral independent PLEDs (BiPLEDs) in a 69-year-old woman with Hashimoto's encephalopathy.*

Among seizure patients, 90% had partial seizures, with focal motor activity proving most common. Epilepsia partialis continua (EPC) occurred in 18 patients. In most of these patients PLEDs were noted on EEG hours to days before the development of EPC. Nine patients had EEGs recorded during ongoing EPC activity. The clonic activity was time-locked with the PLEDs in five of these cases. Partial seizure and EPC activity correlated precisely with PLED localization in all cases.

Convulsive status epilepticus (SE) occurred in 23 patients, and was the presenting complaint in 21 of these. The convulsive status had been successfully treated when the EEG recorded PLEDs. Nonconvulsive status epilepticus (NCSE) occurred in 11 patients (Figure 4). All but one of these patients had electrographic seizure activity recorded on EEG, distinct and evolving from the PLED pattern.

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Table 3: PLED etiologies and subtype in 96 patients

PLED ETIOLOGIES	No. (%)	PLEDS	PLEDS +	BiPLEDs	BiPLEDs +
ACUTE STROKE (CEREBRAL INFARCTION)	**25 (26%)**	**13**	**5**	**6**	**1**
Ipsilateral Stroke (12 Right MCA, 2 Left MCA, 3 Left PCA)	17	13	4	-	-
Bilateral Strokes (3 Watershed, 3 Cardioembolic, 1 Septic Emboli in IE)	7	-	1	5	1
Stroke (Left MCA) + Hypoglycemic Encephalopathy	1	-	-	1	-
TUMOR	**11 (12%)**	**8**	**2**	**1**	**-**
Ipsilateral Meningioma (1 with Bilateral Post-operative ICH)	4	3	-	1	-
Ipsilateral Oligodendroglioma	1	1	-	-	-
Primary CNS B-Cell Lymphoma - Ipsilateral Imaging Focus	4	3	1	-	-
Ipsilateral Solitary Metastasis (Lung Carcinoma, B-Cell Lymphoma)	2	1	1	-	-
ACUTE INFECTION	**11 (12%)**	**7**	**1**	**2**	**1**
HSV Encephalitis - (6 with Ipsilateral Imaging Foci, 2 with Bilateral)	8	5	1	2	-
Adenoviral Encephalitis - No Imaging Focus	1	-	-	-	1
Ipsilateral Bacterial Cerebritis – Infected Ommaya Reservoir	1	1	-	-	-
CNS Toxoplasmosis in End Stage AIDS - Ipsilateral Focus	1	1	-	-	-
ACUTE HEMORRHAGE	**11 (12%)**	**9**	**1**	**1**	**-**
Ipsilateral SDH & Cerebral Contusion	5	4	1	-	-
Ipsilateral ICH 2° to Amyloid Angiopathy	1	1	-	-	-
SAH due to Acom Aneurysm Rupture, 2° Bilateral ACA Infarcts	1	-	-	1	-
Acute Traumatic Brain Injury	4	4	-	-	-
ACUTE DEMYELINATION / MULTIPLE SCLEROSIS	**3 (3%)**	**3**	**-**	**-**	**-**
Multiple Sclerosis exacerbation - Ipsilateral Plaque	2	2	-	-	-
Osmotic Demyelination - Ipsilateral Imaging Focus	1	1	-	-	-
ACUTE HYPOXIC-ISCHEMIC ENCEPHALOPATHY	**3 (3%)**	**1**	**-**	**2**	**-**
Bilateral Imaging Foci (1 Post-Cardiac Arrest, 1 Acute Resp Failure)	2	-	-	2	-
Septic Shock with Multi-Organ Failure - Ipsilateral Remote Stroke	1	1	-	-	-
ACUTE HYPERTENSIVE ENCEPHALOPATHY/ PRES	**3 (3%)**	**3**	**-**	**-**	**-**
Hypertensive Encephalopathy - No Imaging Focus	1	1	-	-	-
PRES - Ipsilateral > Contralateral Imaging Foci	2	2	-	-	-
ALCOHOL-RELATED SEIZURES & CEREBRAL ATROPHY	**6 (6%)**	**5**	**-**	**1**	**-**
CORTICAL DYSPLASIA & REMOTE PATHOLOGY	**9 (9%)**	**6**	**3**	**-**	**-**
Cortical Tuber in Tuberous Sclerosis	1	1 (chronic)	-	-	-
Ipsilateral Hemimegalencephaly & Functional Hemispherectomy	1	1 (chronic)	-	-	-
Ipsilateral Focal Cortical Dysplasia	1	-	1 (chronic)	-	-
Remote Ipsilateral ICH 2° to AVM Rupture	1	1 (chronic)	-	-	-
Ipsilateral Encephalomalacia Post-Tumor Resection & Radiation	2	1 (chronic)	1 (chronic)	-	-
Remote Traumatic Brain Injury - Ipsilateral Contusion	2	1 (chronic)	1 (chronic)	-	-
Cerebral Palsy - Ipsilateral Perinatal Hemorrhage	1	1 (chronic)	-	-	-
MISCELLANEOUS	**12 (12%)**	**7**	**-**	**3**	**2**
Ipsilateral Cavernoma with Acute Intralesional Hemorrhage	2	2	-	-	-
Hepatic Encephalopathy + Remote Ipsilateral SAH & Stroke	1	1	-	-	-
Cerebral Amyloidosis - Multifocal Disease	1	-	-	-	1
Creutzfeldt-Jacob Disease	3	-	-	3	-
Hashimoto's Encephalopathy - No Imaging Abnormalities	1	-	-	-	1
Rasmussen's Encephalitis - Ipsilateral Imaging Focus	1	1	-	-	-
Familial Hemiplegic Migraine	1	1	-	-	-
Ipsilateral Mesial Temporal Sclerosis	2	2	-	-	-
UNKNOWN	**2 (2%)**	**1**	**-**	**-**	**1**

MCA: middle cerebral artery; PCA: posterior cerebral artery; ACA: anterior cerebral artery; IE: infective endocarditis; HSV: herpes simplex virus; SDH: subdural hematoma; ICH: intracerebral hemorrhage; SAH: subarachnoid hemorrhage; PRES: posterior reversible encephalopathy syndrome

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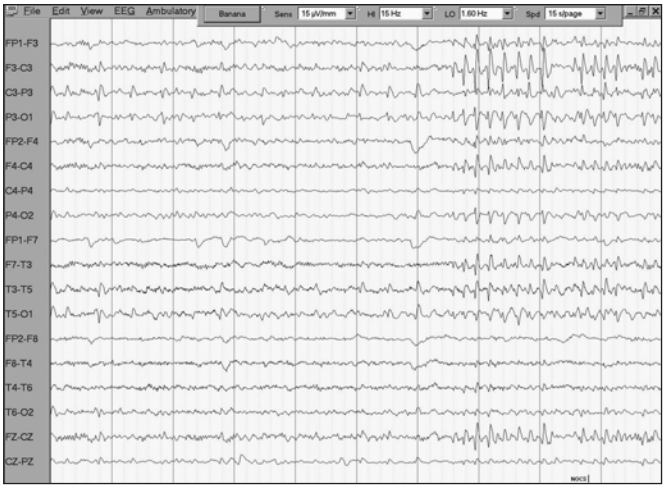

Figure 4: *Nonconvulsive status epilepticus in a 74-year-old man with a traumatic brain injury. Left-sided PLEDs repeatedly evolved into focal electrographic seizure activity of 30-120 seconds duration. The patient remained unresponsive throughout the recording until 3mg of i.v. lorazepam was administered. The PLEDs continued, but seizure activity resolved following lorazepam use.*

Table 4: Metabolic abnormalities in 96 patients with PLEDs †

Persistent or Recurrent Metabolic Abnormality	No. Cases
Hepatic Dysfunction*	17
Acute Renal Failure - CrCl ↓ by > 50%	7
Hypernatremia - Na^+ ≥ 150mmol/L, osm ≥ 301mmol/kg	7
Acidosis - pH < 7.20	5
Hypokalemia - K^+ ≤ 2.5mmol/L	4
Hypomagnesemia - Mg^{2+} ≤ 0.49mmol/L	3
Hypoglycemia - glucose ≤ 2.5mmol/L	2
Hyperosmolar Non-Ketotic State (HONKS) - glucose ≥ 34mmol/L, osm ≥ 336mmol/kg	1
Hypothyroidism - TSH 37.5mIU/L, T4 7.5pmol/L)	1
Hyperkalemia - K^+ ≥ 5.9mmol/L	1
Hyponatremia - Na^+ ≤ 123mmol/L, osm ≤ 259mmol/kg	1

† Present on a persistent or recurrent basis at the time of and during the 36-48 hours preceding the EEG(s) which exhibited PLED phenomenon; * Defined as persistent elevation, ≥ twice the upper limit of normal, in at least 3 of AST, ALT, ALP, GGT; OR enzyme elevation not meeting this requirement combined with 3 of the following 4 criteria: 1.) INR ≥ 1.4 (not on anticoagulation) 2.) Bilirubin ≥ 30μmol/L 3.) Ammonia ≥ 60μmol/L 4.) Albumin ≤ 15g/L

Among patients with BiPLEDs and BiPLEDs Plus, clinical seizures consisted of unilateral (n=6) or bilaterally independent (n=7) focal motor activity, or generalized tonic-clonic activity (n=3). No significant relationship was found between seizure occurrence and PLED etiology. Twenty-three percent of the study group (22 patients) had a preexisting partial seizure disorder. All nine patients with chronic PLEDs were among this subgroup. There were no patients with known history of primary generalized epilepsy. However, seven patients had experienced prior alcohol-related generalized seizures. There was inadequate follow-up data to determine the extent of seizure or PLED recurrence.

The overall mortality rate was 27%. Mortality among patients with BiPLEDs was 52%.

Metabolic Abnormalities and Fever

Fever was present in 40% of cases at the time of PLED occurrence. The most common sources were comorbid pneumonia and urinary tract infection. Significant metabolic abnormalities were present in 35% of cases. These are outlined in Table 4.

Discussion

Periodic lateralized epileptiform discharges are usually seen diffusely over one cerebral hemisphere, but may be localized to a single lobe. They have a frequency of 0.2 to 3 Hz, are often bi, tri- or polyphasic in form, and associated with a localized reduction in the background activity present between discharges.[1-8,17-22,30] Periodicity, the hallmark of PLEDs, generally varies less than 20% within an individual EEG, but may vary significantly from patient to patient.[7,8] PLEDs occupy most, or usually all, of the EEG recording and do not evolve in frequency or location, differentiating this pattern from ictal discharges.[8,19,20] The PLEDs encountered in our study population conformed to these parameters. Periodic lateralized epileptiform discharges are almost exclusively transient in nature, rarely persisting for more than a few weeks. They evolve and abate over an average two week time-frame, with wave forms becoming progressively less complex and frequent over time.[1-8,17-20] In patients with multiple EEGs, excluding cases of chronic PLEDs, this pattern of PLED resolution was evident in all cases. In all nine patients with chronic PLEDs there was marked stability of PLED morphology and periodicity between recordings, in agreement with prior reports.[13] More background slowing was often observed in post-ictal recordings.

Most patients with BiPLEDs had a single, independent PLED focus in each hemisphere, though multifocal PLEDs were noted in two patients. Six of the BiPLEDs patients evolved through a pattern of unilateral PLEDs, with or without independent sharp waves in the contralateral hemisphere, preceding BiPLED development or during its' resolution. This pattern has been previously recognized,[7] though it is uncertain how frequently it occurs. This issue could not be addressed in our study group, as 8 of the 21 BiPLED patients had only one EEG recording. It is worth noting that four of the six BiPLED patients with unilateral focal motor or EPC activity were among those with evolution through a pattern of unilateral PLEDs, which were contralateral to the clonic activity in all cases. Two of the three patients with Creutzfeldt-Jacob disease had follow-up EEGs demonstrating evolution to the classic pattern of generalized periodic complexes (GPEDs) prior to death.

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The overall prevalence of PLEDs encountered, 0.8%, is consistent with reports from other centers, which range from 0.4 to 1%.[1,7,8,18-21] The true incidence is likely higher, as many patients with PLEDs may not receive an EEG, particularly those without seizure or altered level of consciousness. This creates an inherent selection bias toward the sicker patients. The incidence of BiPLEDs in our study group, 22%, was higher than the 4-16% previously reported.[1,7,22,30] This disparity may reflect a trend toward more frequent EEG testing of ICU patients. An 18% incidence of BiPLEDs has been demonstrated among patients with PLEDs recorded during continuous EEG monitoring in the ICU.[31]

Our data concerning PLED etiology largely concurs with that published by other authors, but does add several new entities and provide some new insights. Review of the literature reveals that acute ischemic stroke is the most frequent responsible pathology, followed by tumor and central nervous system (CNS) infection, particularly acute herpes simplex virus (HSV) encephalitis (Table 5).[1-9,12,15-23,30,32,33] Among adults, tumor appears to be a more common etiology than CNS infection, while the reverse is true of pediatric populations, in whom infection may even displace stroke as the primary etiology.

Periodic lateralized epileptiform discharges are reportedly more likely to occur with hemorrhagic transformation of a cerebral infarct and with embolic infarcts.[34] Similarly, more malignant, aggressive tumors appear more apt to produce PLEDs, particularly when a hemorrhagic or necrotizing component is present.[8] Indeed, both hemorrhagic transformation and a cardioembolic source were frequent within our stroke population with PLEDs. At least 13 of the 25 stroke cases were cardioembolic in nature. Most tumor patients had very aggressive malignancies with pathological evidence of hemorrhage and/or necrosis. The four cases of meningioma were distinct in that PLEDs, and seizure, were detected post-operatively, and each was associated with significant operative complications which were the likely cause of the PLEDs.

With the exception of the nine chronic PLED patients and the two cases of undetermined etiology, acute cerebral insults were identified in all but three cases; either an acute structural lesion or an acute infectious, metabolic or toxic insult to the CNS. The

Table 5: Reported PLED etiologies

References	No.	Stroke	Infection	Tumor	Hem*	Metabolic	Anoxia	CJD	?	Other
Chatrian et al. (1964)[1]	33	13	2	8	-	-	-	-	3	7
Markland & Daly (1971)[3]	16	14	2	-	-	-	-	-	-	-
Schwartz et al. (1973)[4]	52	11	2	21	4	-	-	1	1	12
Dauben & Adams (1977)[17]	38	18	4	3	3	2	2	-	-	6
Schraeder & Singh (1980)[18]	24	12	-	3	4	2	3	-	-	-
Kuroiwa & Celesia (1980)[19]	26	11	-	9	3	2	-	-	-	1
Chu (1980)[9]	6	1	1	-	-	-	-	-	-	4
de la Paz & Brenner Ψ (1981)[15]	63	16	7	5	3	3	8	-	5	16
Striano et al. (1986)[6]	20	15	3	1	1	-	-	-	-	-
Walsh & Brenner (1987)[21]	39	13	3	3	1	1	2	1	5	10
Young et al. (1988)[20]	23	10	2	6	2	-	-	-	3	-
Snodgrass et al. (1989)[7]	147	53	12	10	13	22	18	-	-	19
Hamano et al.† (1994)[32]	6	2	3	-	1	-	-	-	-	-
Garg et al. † (1995)[33]	15	3	4	2	1	3	1	-	-	1
Gross et al. (1999)[22]	47	9	7	8	5	3	-	2	-	13
Lawn et al. Ψ (2000)[16]	35	4	7	1	5	7	3	-	-	8
Baykan et al. (2000)[23]	45	10	15	5	2	-	-	1	9	3
Garcia-Morales et al. (2002)[5]	130	61	24	16	18	-	5	3	-	3
Chen et al. † (2003)[30]	44	1	29	-	5	3	1	-	-	5
Gurer et al. (2004)[12]	71	20	16	11	6	2	2	-	1	13
TOTAL	**880**	**297** **34%**	**143** **16%**	**112** **13%**	**77** **9%**	**50** **6%**	**45** **5%**	**8** **1%**	**27** **3%**	**121** **13%**

* All intracranial hemorrhages; including intracerebral, subarachnoid, subdural & epidural (traumatic & non);
Ψ BiPLEDs only; † Children only

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three exceptions included the two patients with mesial temporal sclerosis (MTS) and the patient with familial hemiplegic migraine. The MTS patients presented with an exacerbation of their chronic seizure disorder and exhibited ipsilateral PLEDs for a transient period post-ictally. No metabolic, toxic or infectious process was identified in either case. Although MTS specifically has not been previously reported as a cause of PLEDs, exacerbation of a chronic seizure disorder has frequently been cited as the underlying etiology for PLED development, comprising the majority of the 'other' category in Table 5.[1,4,15,16,21-23,30] In our experience however, it is a rare cause of PLEDs, underscoring the importance of thorough investigation in such patients to exclude a precipitating acute process. The patient with familial hemiplegic migraine had PLEDs contralateral to the migraine-involved hemisphere. She had a longstanding history of recurrent left parietal headaches associated with aphasia, a right hemiparesis and hemisensory deficit, and was positive for the CACNA1A gene mutation. She presented with a typical, though severe, left sided headache and later developed an altered level of consciousness. Electroencephalogram showed right hemisphere PLEDs and intermittent electrographic seizure activity. The seizure activity resolved following lorazepam administration, correlating with return of normal sensorium, but PLEDs persisted. There were no abnormalities or regions of diffusion restriction on MRI. CSF analysis was normal. Transient cerebral ischemia is the postulated mechanism of PLED development in this case.

An acute structural lesion was evident in 68 patients (71%), based on neuroimaging and autopsy findings, in agreement with prior reports.[11,12] Correlation between findings on neuroimaging and PLED localization was excellent. There were no cases with PLEDs contralateral to the responsible structural lesion, though this has been reported.[12] Patients lacking an acute structural lesion included the chronic PLED group (n=9) and the alcohol-related group (n=6), as well as the cases of CJD (n=3), adenoviral encephalitis (n=1), hypertensive encephalopathy (n=1), familial hemiplegic migraine (n=1), Hashimoto's encephalopathy (n=1), and two cases in which an acute anoxic or metabolic insult 'triggered' PLED formation ipsilateral to a remote cerebral lesion. One of these patients had acute hypoxic encephalopathy with PLEDs ipsilateral to a remote stroke; while the other had an acute hepatic encephalopathy heralding PLEDs at the site of a remote stroke and subarachnoid hemorrhage (SAH). This phenomenon of acute PLEDs at the site of a remote structural lesion in the setting of an acute metabolic insult has been previously reported.[7-12,17] This is the presumed mechanism of PLED development in previously reported cases of alcohol withdrawal seizures.[8,9,17] In these prior cases, all had autopsy or imaging-proven preexisting focal lesions ipsilateral to their PLEDs. Alcohol withdrawal then acted as an acute trigger for PLED development at the site of remote pathology. In our study neuroimaging failed to identify such cortical lesions. Our six patients with alcohol-related seizures showed significant cerebral and cerebellar atrophy on neuroimaging, as well as marked subcortical microvascular changes, but no focal or lateralizing features (even in the setting of unilateral PLEDs). This emphasizes that alcohol intoxication or withdrawal alone may be a significant etiologic factor in PLED development. The mechanism of PLED localization in this setting remains uncertain. It is noted however that three of these six patients had CT imaging rather than MRI, and it is possible that a small lesion could have been missed.

Among patients with acute destructive cortical lesions, PLEDs have been reported to occur more frequently in patients with comorbid fever or metabolic abnormalities, such as hyperglycemia.[20,35] Although we did not have comparative control groups in our review, the frequency and severity of metabolic abnormalities and co-existent fever in our patient series were remarkable and likely supports this premise.

Although PLEDs, and particularly PLEDs Plus, are highly correlated with clinical seizure activity, they are generally not considered an ictal EEG pattern.[20] Patients have been described with a transient confusional state and PLEDs on EEG, thought to represent a form of nonconvulsive status epilepticus.[25-27] The EEG pattern described in these reports, however, is generally not that of typical PLEDs. Drury et al report four cases having either intermittent bursts of GPED activity with intervening segments of normal EEG, or PLED-like activity which abated following administration of intravenous benzodiazepine.[25] Beaumanoir et al. detail a unique PLED-like pattern they term 'periodic sinusoid paroxysmal activity' (PSPA) which may be associated with a transient confusional state.[27] Increased regional cerebral blood flow and glucose metabolism have been demonstrated on PET and SPECT scanning during PLEDs.[28,29] Because this is also seen during seizures, this finding has been used to support claims of an ictal PLED nature. However, it can be argued that this is only a marker of increased neuronal activity, and not seizure activity per se. The most convincing argument that PLEDs may, in some cases, be ictal is derived from the occasional association with time-locked EPC.[7,8,19,23]

The strong association between PLEDs and seizure occurrence is well demonstrated in our study and stresses the importance of anticonvulsant use in all patients with PLEDs. Chong and Hirsch propose one month of prophylactic anticonvulsant use in all patients with PLEDs, irrespective of seizure occurrence, and a course of 3-12 months in all patients with documented seizures, recognizing that longer courses or lifelong treatment may be required in some cases.[36] The high rate of NCSE lends convincing support to the argument for continuous EEG monitoring in ICU patients. In a recent study, 73% of children found to have PLEDs on continuous EEG monitoring in the ICU experienced nonconvulsive seizure activity, despite what was clinically felt to be adequate anticonvulsant treatment.[37] More than 24 hours was often required to detect this activity. The longer recurrent nonconvulsive seizure activity or NCSE persist, the more difficult they are to treat and the higher the associated morbidity and mortality.[38] Indeed, this case series emphasizes that despite advances in neurocritical care, the morbidity and mortality associated with PLEDs has changed little since their recognition four decades ago. This was even more striking in the BiPLEDs group, where the mortality rate was 52%. It is hoped that future controlled, prospective trials will better delineate the underlying pathophysiology of PLEDs and their relationship to seizures, and provide insight into avenues for improved management.

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