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Generalised periodic epileptiform discharges: clinical features, neuroradiological evaluation and prognosis in 37 adult patients☆

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Generalised periodic epileptiform discharges (GPEDs) are very rare patterns and are classified as periodic short-interval diffuse discharges (PSIDDs), periodic long-interval diffuse discharges (PLIDDs) and suppression-burst patterns according to the interval between the discharges.

In this study we analysed the demographics, history of the seizures during the current illness, mental status, diagnosis, metabolic abnormalities, neuroimaging studies and prognosis of 37 adult patients who had GPEDs in their EEGs. Ages ranged from 17 to 82 years (mean 45 years). There were 19 males and 18 females. The most common aetiology of GPEDs was metabolic and/or infectious disease which was established in 22 patients (59.5%). Other aetiologies included subacute sclerosing panencephalitis (SSPE) in 11 patients (29.7%) and Creutzfeld–Jakob disease (CJD) in 4 patients (10.8%). We showed that structural lesions were found in most of the patients with GPEDs, but concurrent metabolic abnormalities and/or infectious diseases were also detected. Consciousness was impaired and clinical conditions were poor in various degrees in all of the patients when GPEDs were seen. Relatively little is known regarding the mechanism of GPEDs.

When GPEDs are seen in EEG, the patient should carefully be checked for metabolic abnormalities and/or infectious diseases and intracranial lesions. GPEDs may be helpful in the determination of prognosis, showing the poor prognosis especially in cases when suppression-burst pattern is seen.

Key words: EEG; generalised periodic epileptiform discharges; neuroimaging; adults; seizures; prognosis.

INTRODUCTION

The term ‘periodic’ refers to activity that is regularly recurrent in EEG; applies to waves or complexes occurring in sequence at an approximately regular rate or intermittently at approximately regular intervals[1]. Periodic patterns usually occupy most of a standard EEG rather than appearing as a transient portion[2,3].

These complexes can be classified according to their distribution. If periodic complexes are limited to a focal brain area (often one hemisphere) they are known as periodic lateralised epileptiform discharges (PLEDs)[4]. PLEDs have been the focus of many reports and much have been written about the aetiology and pathogenesis[5,6]. When periodic complexes that occupied at least 50% of a standard 20 min EEG, occur over both hemispheres in a symmetric, diffuse and synchronised manner, they are known as generalised periodic epileptiform discharges (GPEDs)[2,5]. GPEDs are very rare patterns.

To classify these GPEDs, the interval between the discharges are used. Periodic short-interval diffuse discharges (PSIDDs) are the discharges with the interval duration 0.5–4 seconds. They occur in hypoxic or hepatic encephalopathy, drug toxicity, degenerative disorders such as Creutzfeldt–Jakob disease (CJD)[5]. PSIDDs due to anoxia were reported to be associated with a fatal outcome or severe neurological sequeals especially if it is associated with repetitive myoclonic jerks[7–9]. Periodic long-interval diffuse discharges (PLIDDs) are the discharges with the interval duration 4–30 seconds[5]. The complexes are polyphasic,

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containing an admixture of frequencies, including sharp components, and delta activity. They were detected mostly in subacute sclerosing panencephalitis (SSPE), drug toxicity and less commonly in hypoxic encephalopathy[2, 5, 10, 11]. Suppression-burst pattern is considered as a third group. Suppression-burst pattern is defined as high-voltage bursts of slow waves with intermingled sharp transients or spikes occur against a depressed background or complete flatness. The bursts are quasi-periodically repeated and frequently, but not invariably, accompanied by diffuse myoclonic jerks[12, 13]. Many records of deeply comatose patients are characterised by a suppression-burst pattern[14]. Suppression-burst pattern often occur in hypoxic encephalopathy or drug overdose, particularly barbiturates or administration of anaesthetics such as sodium pentothal[2, 5].

In literature, there is no study with large number of patients having GPEDs excluding drug related or iatrogenic reasons and whose both neuroimaging studies were examined and metabolic abnormalities were evaluated. This study was designed to investigate the structural lesions in patients who had GPEDs and to determine the possible relation of metabolic abnormalities, intracranial structural lesions, and diagnosis to GPED patterns, clinical features, seizure type and prognosis. There are many questions about the pathogenesis of GPEDs. The roles of the structural lesions and/or metabolic abnormalities are still unresolved.

PATIENTS AND METHODS

All EEGs of the adult patients, performed at Hacettepe University, Neurology Department between 1992 and August 2000 were reviewed and those with GPEDs were established. GPEDs were defined as the occurrence of periodic complexes occupying at least 50% of a standard 20 minutes EEG, over both hemispheres in a symmetric, diffuse and synchronised manner[2, 5]. Then we classified these generalised periodic patterns according to the interval duration between the discharges. If the interval duration of the discharges were 0.5–4 seconds they were defined as periodic short-interval diffuse discharges (PSIDDs) (Fig. 1). If the interval duration of the discharges were 4–30 seconds they were defined as periodic long-interval diffuse discharges (PLIDDs)[5] (Fig. 2). Suppression-burst patterns were defined as high-voltage bursts of slow waves with intermingled sharp transients or spikes occur against a depressed

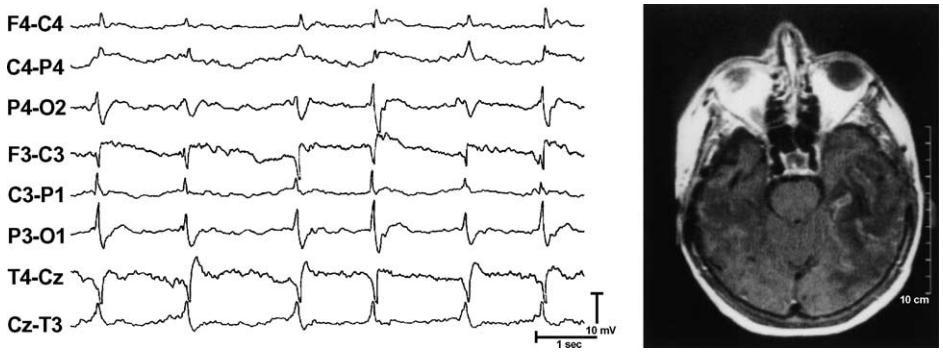

Fig. 1: Seventy-five years old female with herpes encephalitis and hypernatremia. EEG shows PSIDDs. Cranial MRI shows bilateral concurrent cortical and subcortical lesions.

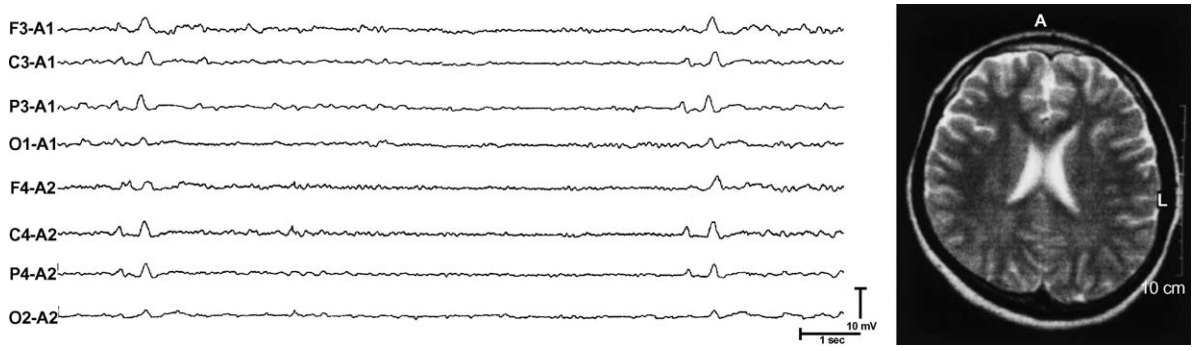

Fig. 2: Eighteen years old male with SSPE. EEG shows PLIDDs. Cranial MRI shows bilateral parieto-occipital periventricular subcortical hyperintense lesions.

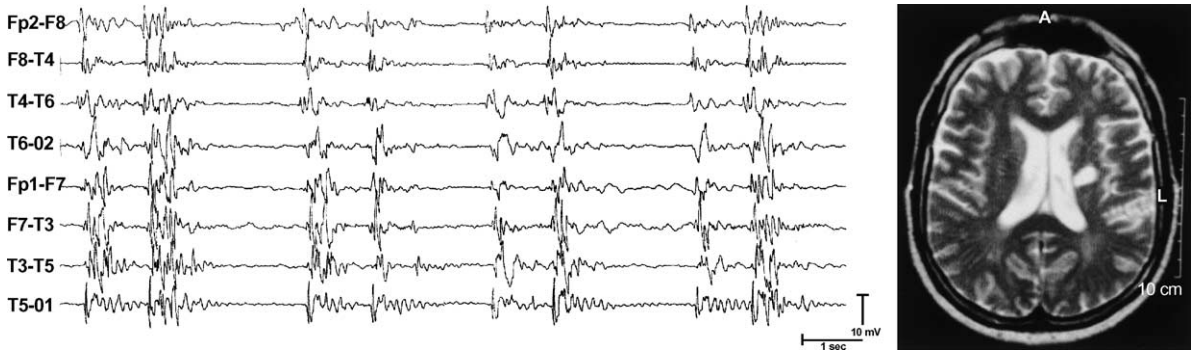

Fig. 3: Fifty-three years old male diagnosed as hypoxic encephalopathy, EEG shows suppression-burst pattern. Cranial MRI shows multiple concurrent cortical and subcortical lesions consistent with chronic infarctions.

background or complete flatness (Fig. 3). Available medical reports and neuroradiological evaluations of the patients with GPEDs were reviewed and noted on a data sheet. Iatrogenic GPEDs (e.g. caused by thiopental) were excluded in this study.

All patients had eight-channel EEGs performed according to the International 10-20 system of electrode placement instrument equipment (Grass model 6) with a minimum of 21 electrodes. Additional leads were applied in selective cases. Recordings included both bipolar and referential montages, using as reference ipsilateral ear electrodes. Activation procedures included photo stimulation and hyperventilation if the patients were co-operated.

Patient demographics, history of the seizures during the current illness, mental status, diagnosis at the time of the EEG, metabolic studies, neuroimaging studies and prognosis of the patients with GPEDs were determined.

A patient was considered to be in status epilepticus (SE) if the EEG showed unequivocal electrographic seizure activity or the patient had clinical (tonic–clonic) seizure activity during the EEG.

The presence or absence of structural abnormalities of the brain was determined by brain computerised tomography (CT) or magnetic resonance imaging (MRI). CT was held with 5-mm axial slices from orbitomeatal line to vertex. MRI was performed with 0.5 T with a 30-cm diameter head coil. Multiplan MRI scans were T2-weighted, T1-weighted, FLAIR and proton density. Axial, coronal and sagittal planes were displayed. Contrast medium was given intravenously if indicated. Scans included in the analysis were classified as normal or abnormal. Those with abnormal findings were categorised by lesion localisation as: (a) cortical; (b) subcortical; (c) concurrent cortical and subcortical lesions.

Blood samples for complete blood count and for blood levels of glucose, calcium, electrolytes were held. Measles antibody titres were obtained from blood and cerebrospinal fluid (CSF) in the patients suspected of having SSPE. Viral antibody titres of blood and CSF were studied in the patients with suspected encephalitis. Diagnosis of CJD was made clinically as they were the typical cases with dementia, myoclonus, periodic EEG and fatality. Autopsy could be done in only 1 of the 4 CJD diagnosed patients.

The aims of the study were as follows:

1. To detect the localisations of the intracranial lesions of patients with GPEDs (cortical, subcortical or concurrent cortical and subcortical).
2. To find out if the any pattern or interval could suspect the lesion type and prognosis.
3. To determine if the patient had seizure when EEG was performed.
4. To observe if metabolic deficits of patients affect GPED formation in patients with and without intracranial lesions.
5. To follow up the prognosis of patients with GPEDs.

RESULTS

Thirty-seven patients were included in this study. Ages ranged from 17 to 82 years (mean 45 years). There were 19 males and 18 females.

Aetiology

The most common aetiology (Table 1) of GPEDs was metabolic and/or infectious disease which was established in 22 patients (59.5%). Other aetiologies included SSPE in 11 patients (29.7%) and CJD in 4 patients (10.8%). Metabolic and/or infectious diseases

Table 1: Aetiology of GPEDs in 37 adult patients.

Aetiology	Number of patients (%)
Metabolic and/or infectious disease	22 (59.5)
Hypoxic encephalopathy	7
Hyponatremia	2
Uremia	2
Sepsis	2
Sepsis + DIC	2
Sepsis + uremia	1
Sepsis + uremia + DIC	1
Herpes encephalitis + hypernatremia	1
Hepatic encephalopathy	1
Hepatic encephalopathy + hyponatremia	1
Hepatic encephalopathy + uremia	1
Hyponatremia + ketoacidosis + infection	1
SSPE	11 (29.7)
CJD	4 (10.8)
Total	37 (100)

included hypoxia in 7 patients, hyponatremia in 2 patients, uremia in 2 patients, sepsis in 2 patients, sepsis and DIC in 2 patients, sepsis and uremia in 1 patient, sepsis and uremia and DIC in 1 patient, herpes encephalitis and hypernatremia in 1 patient, hepatic encephalopathy in 1 patient, hepatic encephalopathy and hyponatremia in 1 patient, hepatic encephalopathy and uremia in 1 patient, hyponatremia and diabetic ketoacidosis and systemic infection in 1 patient.

Neurological symptoms

Consciousness was impaired to some degree in all of the patients when GPEDs were detected in their EEGs. Fifteen patients (40.5%) were in comatose state; and 22 patients (59.5%) were lethargic or stuporous.

Association with seizures

Thirty-three patients (89.2%) had seizures within 48 hours of EEG detection of GPEDs. The types of the seizures are shown in Table 2. Thirteen patients (35.2%) had only myoclonic jerks (MJs). Twelve patients (32.4%) were in SE when EEG were established. Eight patients (21.6%) had only generalised tonic–clonic seizures (GTCS). Four patients (10.8%) had no clinical epileptic seizure. Three of the patients without any epileptic seizures had metabolic abnormality and/or infectious disease and concurrent cortical and subcortical lesions on their cranial MRI and the other one was autopsy proven CJD having a normal CT scan.

Table 2: The type of the seizures within 48 hours of EEG detection of GPEDs.

Seizures	Number of patients (%)
Myoclonic jerks (MJs)	13 (35.2)
Status epilepticus	12 (32.4)
Generalised tonic–clonic seizures (GTCS)	8 (21.6)
No seizure	4 (10.8)
Total	37 (100)

Neuroimaging

Neuroradiological evaluation was made in 28 patients (75.7%) (Table 3). Eighteen (64.3%) had cranial MRI scans and 10 (35.7%) had cranial CT scans. No imaging was performed in 9 patients (24.3%) due to their poor clinical conditions. Although CT scans may have inadequate resolution for lesion localisation, again due to the patients' poor clinical conditions, 10 had only CT scans. Concurrent cortical and subcortical lesions were established in 14 patients (50%). Only subcortical lesions were established in 7 patients (25%). Only cortical lesions were established in 1 patient (3.6%). Normal MRI or CT was present in 6 patients (21.4%).

Metabolic and/or infectious diseases were detected in 16 patients (57.1%) who had neuroradiological evaluation. Twelve patients (42.9%) had no metabolic and/or infectious disease within 24 hours after GPEDs plotted on EEG.

EEG features and prognosis

EEG features according to aetiologies and prognosis are seen in Table 4. PSIDD was detected in 15 patients (40.5%). No lesion could be found in 4 of them. Eleven had metabolic and/or infectious disease and four was diagnosed as CJD. Mortality within the first month was 53.3% in patients with PSIDD.

PLIDD was seen in 15 patients (40.5%). Neuroradiological evaluation was found normal in 2 of them. Eleven were diagnosed as SSPE and 4 had metabolic and/or infectious disease. Mortality within the first month was 20% in patients with PLIDD.

Suppression-burst pattern was seen in 7 patients (18.9%). Three of them had hypoxic encephalopathy. Sepsis was present in the other three either alone or with DIC or with DIC and uremia. The last one had only hyponatremia. Mortality within the first month was 100% in the patients with suppression-burst pattern and after the pattern was seen on EEG, 85% died within the first week.

The overall mortality within the first month, after GPEDs were seen on EEG was 48.7%.

Table 3: The characteristics, aetiology, neuroimaging and GPED patterns in the patients who had neuroradiological evaluation.

Number	Age	Sex	Aetiology	Neuroimaging (MRI/*CT)	EEG
1	75	F	Herpes encephalitis, hypernatremia	High signal intensity on T2-weighted images of bilateral cortical and subcortical frontal, temporal regions with contrast enhancement	PSIDD
2	35	F	Hepatic encephalopathy, uremia	Multiple cortical and subcortical ischemic gliotic lesions	PSIDD
3	56	F	Ketoacidosis, hyponatremia, infection	Multiple subcortical ischemic gliotic lesions	PSIDD
4	18	M	Cerebral palsy, mental-motor retardation, sepsis, DIC	*Hyperdense lesion on the left parietal lobe due to chronic, large infarction	PSIDD
5	40	M	Chronic renal failure, uremia	*Bilateral cortical and subcortical occipital hypodense lesion	PSIDD
6	82	F	Cardiac arrest, hypoxic encephalopathy	*Cerebral and cerebellar atrophy, multiple, cortical, subcortical, chronic infarctions in occipital, temporal, parietal regions	PSIDD
7	58	F	Hyponatremia	*Normal	PSIDD
8	68	M	Leukaemia, sepsis	*Normal	PSIDD
9	52	M	Chronic renal failure, uremia	*Normal	PSIDD
10	57	F	CJD	Cerebral and cerebellar atrophy and high signal intensity on T2-weighted images in periventricular regions of both hemispheres	PSIDD
11	65	F	CJD	Cerebral and cerebellar atrophy and multiple cortical and subcortical ischemic gliotic lesions	PSIDD
12	55	M	CJD	Cerebral and cerebellar atrophy	PSIDD
13	72	M	CJD (autopsy proven)	*Normal	PSIDD
14	66	F	Multiinfarct dementia, sepsis	Cerebral and cerebellar atrophy and multiple chronic cortical and subcortical infarctions	PLIDD
15	73	F	Sepsis, uremia	Cerebral and cerebellar atrophy and multiple cortical and subcortical infarctions	PLIDD
16	41	F	Breast cancer, hepatic encephalopathy, hyponatremia	Bilateral cortical and subcortical occipital hypointense lesions (supporting posterior leucoencephalopathy syndrome PLES)	PLIDD
17	19	F	SSPE	High signal intensity on T2-weighted images of cortical and subcortical occipital regions of both hemispheres	PLIDD
18	18	M	SSPE	High signal intensity on T2-weighted images of subcortical parietal and occipital periventricular regions of both hemispheres	PLIDD
19	18	F	SSPE	High signal intensity on T2-weighted images of subcortical parietal and occipital periventricular regions of both hemispheres	PLIDD
20	19	M	SSPE	High signal intensity on T2-weighted images of subcortical parietal regions and basal ganglia of both hemispheres	PLIDD
21	22	M	SSPE	High signal intensity on T2-weighted images of cortical and subcortical occipital regions of both hemispheres	PLIDD
22	28	M	SSPE	High signal intensity on T2-weighted images of subcortical parietal and occipital periventricular regions of both hemispheres	PLIDD
23	18	F	SSPE	Normal	PLIDD
24	24	M	SSPE	*Normal	PLIDD
25	53	M	Recent stroke, cardiac arrest, hypoxic encephalopathy	Multiple, chronic, cortical and subcortical ischemic gliotic lesions	Suppression-burst
26	52	F	Cardiac arrest, hypoxic encephalopathy	*Cerebral and cerebellar atrophy, multiple subcortical, chronic infarctions	Suppression-burst
27	20	F	Stroke, hyponatremia	Multiple, chronic, subcortical ischemic gliotic lesions	Suppression-burst
28	62	M	Chronic renal failure, sepsis, uremia, DIC	*Multiple, subcortical, chronic infarctions and leukoaraiosis	Suppression-burst

Table 4: Aetiology and prognosis according to the EEG patterns.

Pattern	Hypoxic encephalopathy	Metabolic and/or infectious disease	SSPE	CJD	Total	Mortality within the first month (%)
Suppression-burst	3	4	–	–	7	100[a]
PSIDD	3	8	–	4	15	53.3
PLIDD	1	3	11	–	15	20
Total	7	15	11	4	37	48.7

[a] 85% within the first week.

DISCUSSION

In our outpatient EEG laboratory, approximately 2500–3000 EEGs have been performing per year. Only 37 patients were found to have GPEDs in their EEGs within the last 8 years. Kuroiwa and Celesia reported that they found periodic patterns in only 62 patients among 15,202 patients who had EEG in 5.5 years time. Among them only 36 met the criteria for GPEDs. In other words GPEDs are very rare patterns.

Although there are some studies, which analysed PLEDs in literature, there are few studies about the morphology of GPEDs and their association with patients' clinical history, diagnosis, metabolic state, and neuroimaging techniques for localisation of the intracranial lesion, association with seizures and prognosis. Occurrence of GPEDs were reported in diseases or conditions affecting the cerebral functions such as metabolic encephalopathy, hypoxia, SSPE, general anaesthesia, drug intoxication, viral encephalitis, CJD, Alzheimer's disease[2, 15].

PSIDDs are one of the groups of GPEDs[5]. In our study PSIDDs are seen in 15 patients. Although PSIDDs are generally known as seen in CJD, most of our patients had hypoxic or metabolic and/or infectious disease.

PLIDDs are another group of GPEDs. In our study, PLIDDs are seen in 15 patients. PLIDDs pattern of GPEDs are frequently associated with SSPE and less commonly metabolic encephalopathy which is parallel with literature.

Suppression-burst pattern often occur in anoxic encephalopathy or drug overdose[2, 5]. As in our study we excluded the patients getting these drugs or under anaesthesia, this pattern was found in patients with hypoxic or metabolic encephalopathy. It was reported by several investigators that the presence of suppression-burst pattern in the EEG of adult patients were one of the most reliable prognostic indicators of an unfavourable outcome. Some investigators stated that the mortality rate was 96% and some 100%[2, 16, 17]. As in prior studies, mortality within the first month was found to be 100% in this study. Eighty-five percent of these patients died within the first week when this pattern was detected on their EEGs. In patients with hypoxia or sepsis, in whom GPEDs were seen, appear to be representing terminal brain damage[5, 16]. In patients with PSIDDs the mortality was relatively high (53.3% within the first month) when compared to patients with PLIDDs (20%). The possibility of drug effect must always be excluded before it is suggested that this pattern indicates hypoxic encephalopathy as this pattern carries a grave prognosis. However, Nei *et al*. found that GPEDs were associated with a poor outcome independent of aetiology[18]. The pathophysiological mechanism of GPEDs is unknown. Metabolic abnormalities are suggested to play the primary role for GPEDs. The cases that show no structural lesions either post-mortem or at autopsy are indicated by those who propose the primary role for only metabolic abnormality[6, 19, 20].

Raroque and Purdy published the first study correlating PLEDs and the structural lesions by neuroimaging studies. They stated that the structural lesions causing PLEDs were grey plus white matter lesions or only grey matter lesions[21]. However, with the development of neuroimaging techniques it is now possible to demonstrate structural lesions in most of the patients with GPEDs also. To our knowledge there is not any study investigating the role of structural lesions in patients with GPEDs. In our study we found structural lesions in 78.6% of the patients and the most common lesions were subcortical lesions, which were detected in 75% of the patients either alone (25%) or together with cortical lesions (50%) suggesting the role of subcortical involvement in the pathogenesis of GPEDs.

Certain severe metabolic abnormalities are known to be epileptogenic or at least to produce background EEG changes. Metabolic and/or infectious abnormality was detected in 59.5% of the patients in our study. Concurrent structural lesion and metabolic abnormality was detected in 59.1% patients. Current data suggest that in most of the patients, both the concurrent involvement of cortical and subcortical lesions and/or metabolic disturbances seem to play role in the pathogenesis of GPEDs.

In this study most of the patients (89.2%) had seizure within 48 hours of EEG detection of GPEDs. Twelve patients (32.4%) were in SE when EEG were established. Nei *et al*. reported that periodic epileptiform discharges (PEDs) were the only EEG feature related to outcome in SE and are associated with poor

outcome independent of aetiology[18]. If PEDs were present at any time during or after SE, outcome tended to be worse. Brenner reported in a recent study that a number of EEG patterns including GPEDS have been described in non-convulsive (NC) SE, and noted that the diagnostic criteria for NCSE also are controversial, and there are no agreed-on criteria to diagnose NCSE in obtunded/comatose patients, furthermore, outcome is poor[22]. Although some authors have thought that GPEDs may represent NCSE, some thought it as an epileptic encephalopathy, which reflect severe brain injury without impairment in clinical function[23, 24].

Since the descriptions of periodic EEG findings in certain diseases, the electroencephalographers have attempted to explain the mechanism underlying these phenomena[5]. For the mechanism of periodicity, cortical isolation theory has been proposed first by Cobb and Hill[10]. It was suggested that periodic complexes in different clinical states might result from damaged white matter causing an anatomical or functional separation of cerebral cortex from normal afferent input. This theory is considered to be historically interesting now. Raroque *et al*. recently reported structural lesions causing dysfunction of the cortex and adjacent white matter in patients with PLEDs—which are one of the periodic discharges—which is also against this theory[21, 25, 26].

A variety of insults to the brain may result in GPEDs. Gloor *et al*. proposed an abnormal functional state in the central nervous system permitting rapid generalisation of neuronal discharges[27]. Some investigators suggested that synchrony and periodicity may be related to virus-induced fusion of neuronal processes leading to electrotonic coupling between cells as GPEDs are commonly detected in viral diseases such as SSPE and CJD[28, 29]. Secondary to hypoxia, similar pathologic changes have also been observed[2, 30]. However, there must be an event leading to each discharge. Brainstem structures were suggested to act as a pacemaker by some investigators studying about the discharges in SSPE[31]. Some others suggested that GPEDs arise from a subcortical source in CJD[32, 30].

Besides there must be some form of diffuse increase in cortical excitability leading to a predisposition for a burst discharge[5]. Several viral diseases frequently cause periodicity raises the possibility of viral affect on membrane structures via receptors or indirectly through gene transcription. Metabolic, toxic or infectious diseases may also affect the receptor functions which in turn causes periodicity[5]. The periodicity may result from alterations in neuronal excitability which changes the responses to inputs from distant areas. These alterations are thought to have biochemical or anatomical basis[5].

In conclusion, our study is the first specific attempt to define lesion localisation in patients with GPEDs. We showed that structural lesions were found in most of the patients with GPEDs that is new to literature, but concurrent metabolic abnormalities and/or infectious diseases were also detected. Relatively little is known about regarding the mechanism of GPEDs. When GPEDs are seen in EEG, the patient should carefully be checked for metabolic abnormalities and/or infectious diseases and intracranial lesions. Consciousness was impaired and clinical conditions were poor in various degrees in all of the patients when GPEDs were seen. GPEDs may be helpful in the determination of prognosis, showing the poor prognosis especially in cases when suppression-burst pattern is seen[14].

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