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Is There a Final Common Pathway for Malignisation in Different Kind of Epilepsies? Electrographic Features and Clinical Correlations of Generalized Repetitive Fast Discharge (GRFD)

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ÖZET

Değişik Tipteki Epilepsilerde Maliniteye Dönüşü Gösteren Ortak Bir Yol mu Var? Jeneralize Tekrarlayıcı Hızlı Deşarjın (JTHD) Elektrografik Özellikleri ve Klinik Korrelasyonları

Son 10 yılda geçici veya kalıcı "Jeneralize tekrarlayıcı hızlı deşarjlar (JTHD)" (23 hasta) veya lokalize tekrarlayıcı hızlı deşarjlar (LTHD) (6 hasta) gösteren 29 hastanın klinik ve EEG verilerini analiz etmek için retrospektif bir çalışma yapılmıştır. Hastaların çoğu tarafımızdan 10 ile 30 yıl süreyle izlenmiştir. Elektroklinik gelişme şu dağılımı göstermiştir: 8 hasta erişkin çağda da devam eden Lennox-Gastaut sendromu (LGS), 5 hasta jeneralize epilepsinin (JE) erken dönemde ortaya çıkan özellikleriyle geç LGS (GLGS), 10 hasta JE (5 hasta) ve parsiyel epilepsiden (PE) (5 hasta) dönüşen sekonder jeneralize epilepsi (SJE) ve 6 hasta daha önce LTHD görülmeyen, sonradan LTHD oluşan PE'li hastalardır. JTHD gelişen PE'li hastalar JTHD ortaya çıkmadan önce diken-dalga senkronizasyonu göstermişlerdir.

Tüm hastalarda JTHD yavaş uykuda saptanabilirken 15 hastada uyanıklıkta da belirlenmiştir. 15 hastada tonik aksiyel nöbetler veya tonik aksiyel nöbetlerin bazı elemanları JTHD paterniyle direkt ilişkili olarak gözlenmiştir.

JTHD'un frekansı 9 ile 22 Hz arasında değişmekte olup, 10 ile 15-16 Hz arasında 2 tepe yapmaktadır (ortalama: 13.1). Frekans LGS'nda en yüksek, PE grubunda en düşük olarak belirlenmiştir. Epilepsi ne kadar erken yaşta başlarsa frekans o kadar yüksek olmaktadır. Paternin süresi 2 ile 18 saniye arasında değişmektedir. Ortalama süre LGS'da en uzun PE'de en kısa olarak bulunmuştur. Topografik haritalama yapıldığında, JTHD değişken, ünilateral lokal preponderansa sahip, frontal bilateral negatif maksima göstermiştir. On hasta intravenöz benzodiazepin ve heksobarbitalle test edilmiştir. Kronik, yüksek düzeyli benzodiazepin ve/veya fenobarbital tedavisi sırasında benzodiazepin ve heksobarbitalin her ikisinin de patern üstünde, flumazenil ile antagonize edilebilen paradoks aktive edici bir etkisi bulunmaktadır.

JTHD'nin değişik tip epilepsilerde maliniteye dönüşte ortak bir yol niteliğinde olduğu öne sürülmektedir. Bu şekilde bir gelişmeye, sekonder bilateral diken-dalga senkronisinin yayılımından sonra ikinci basamak olarak lokal GABAerjik inhibisyonun bozulmasının yol açtığı varsayılmaktadır. Bu tip bir maliniteye dönüşüm tarafımızdan "Lennoksizasyon" olarak isimlendirilmiştir.

Anahtar sözcükler: *Jeneralize tekrarlayıcı hızlı deşarj (JTHD), epilepsinin gelişimi, Lennoksizasyon, tonik aksiyel nöbetler*

SUMMARY

A retrospective study was performed to analyse the clinical and EEG data of 29 patients exhibiting "generalized repetitive fast discharges" (GRFD) (23 patients) or localized repetitive fast discharges (LRFD) (6 patients) transiently or permanently in the last 10 years. Most of the patients were followed by us from 10 to 30 years. The electroclinical evolution showed the followed distribution: 8 patients had Lennox-Gastaut syndrome (LGS) persisting in adulthood, 5 patients had late LGS (LLGS) earlier exhibiting features of generalized epilepsy (GEP) 10 patients had secondary generalized epilepsy (SGEP) evolved from GEP (5 patients) and from partial epilepsy (PE) (5 patients), and 6 patients had PE with LRFD having earlier PE without LRFD. PE patients where GRFD developed showed spike-wave synchronisation before GRFD appeared.

In all the patients GRFD could be detected during slow wave sleep, and in 15 patients some time in awake state too. In 15 patients tonic axial seizures or some fragments of tonic axial fits could be observed directly in correlation with the GRFD pattern. The frequency of GRFD varied from 9 to 22 Hz (average: 13.1), with two peaks around 10 and 15-16 Hz, highest in classic LGS and lowest in PE group. The earlier the start of epilepsy the higher the frequency was. The duration of the pattern varied from 2 to 18 seconds. The longest average duration was found in LGS and the shortest

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in PE group. The localization of GRFD studied by topographical mapping showed frontal bilateral negative maxima with variable unilateral local preponderance. Ten patients were tested by intravenous benzodiazepines and hexobarbital. During chronic high level benzodiazepine and/or phenobarbital treatment both benzodiazepines and hexobarbital had a paradox activating effect on the pattern antagonised by flumazenil.

GRFD is proposed to assign a common final route of malignisation for different kind of epilepsies. During the course of this kind of progression breakdown of GABAergic local inhibition as a second step after progagation in the form of secondary bilateral spike-wave synchrony is assumed. This type of malignant evolution was designated by us as "lennoxisation".

Key words: *generalized repetetive fast discharge (GRFD) evolution of epilepsy, Lennoxisation, tonic axial seizures*

INTRODUCTION

We have to face up to the fact that epilepsy could be a progressive disease. The physiopathogenesis of the malignant course are not fully explored. The basic feature which seems to differentiate Lennox-Gastaut syndrome (LGS), a highly malignant and therapy resistant epileptic syndrome of childhood from other epilepsies is the development of tonic axial seizures with generalize repetitive fast discharges (GRFD). Assuming that the key element of LGS type malignisation (named by us as "Lennoxisation"), is the development of GRFD, we decided to search for this particular pattern retrospectively in our material in the last ten years. The data of 23

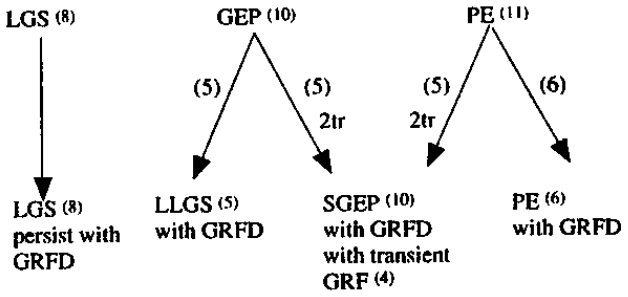


Fig. 1. Evolution of epilepsy syndromes with RFD

patients with GRFD were analysed. In this paper the place of this pattern in different epileptic mechanisms will be treated providing arguments in favour that it could be a common end station in the process of malignisation of different kinds of epilepsies;

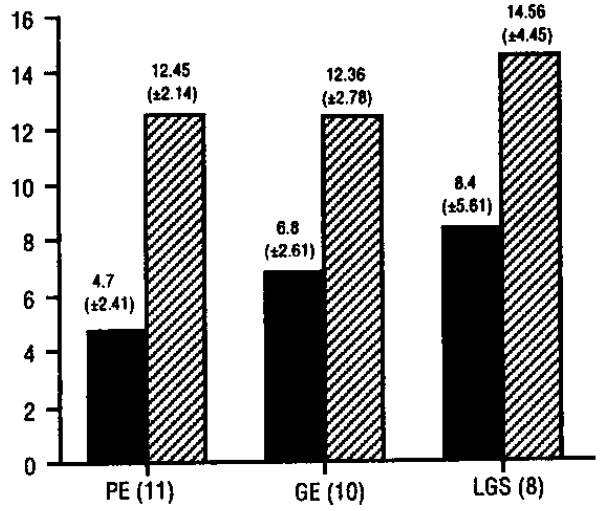


Fig. 3. Duration and frequency of repetitive fast discharges according the original type of epilepsies.

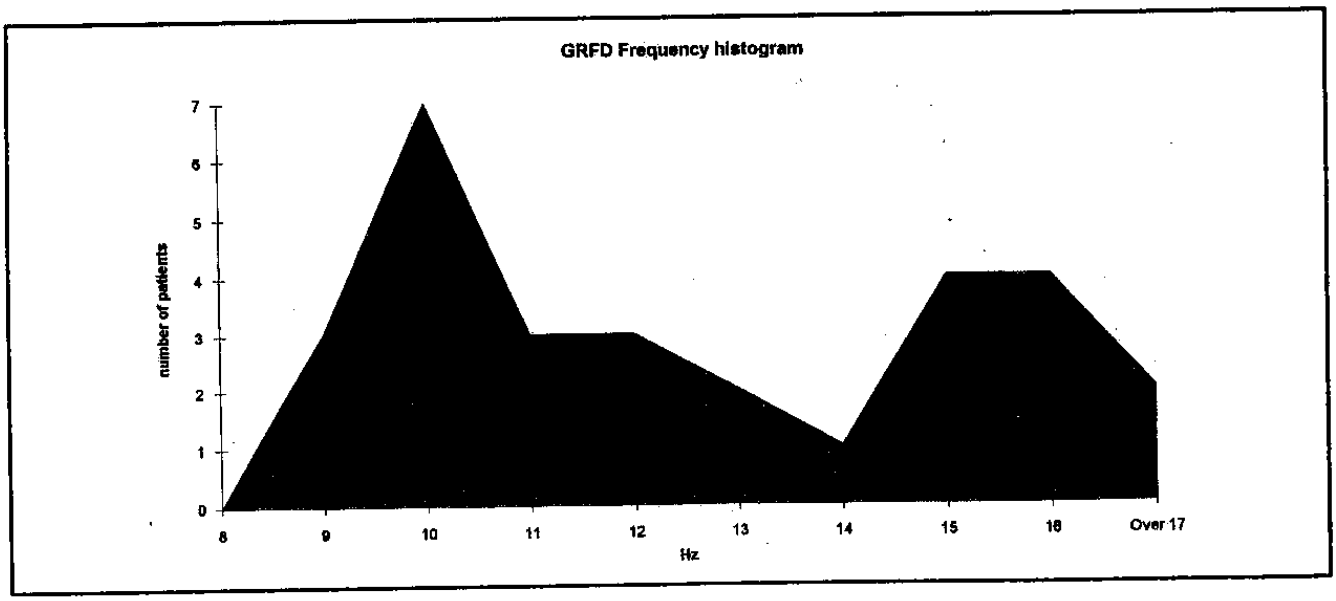


Fig. 2. GRFD frequency histogram.

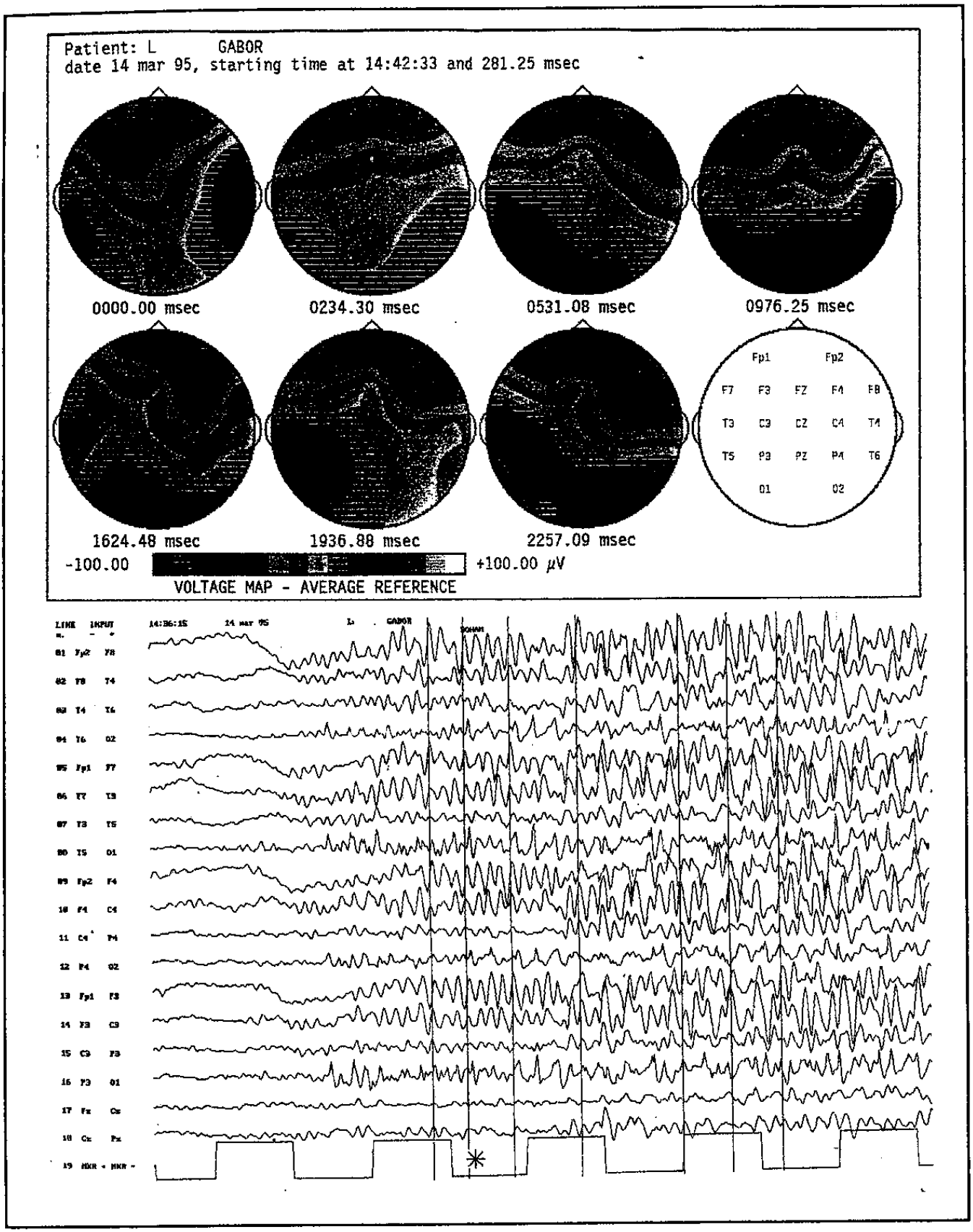


Fig. 4. Serial voltage map taken in ascending slopes before the peak of different waves along the course of the GRFD pattern. There is a bifrontal negative field with variable hemispherial preponderance and extension.

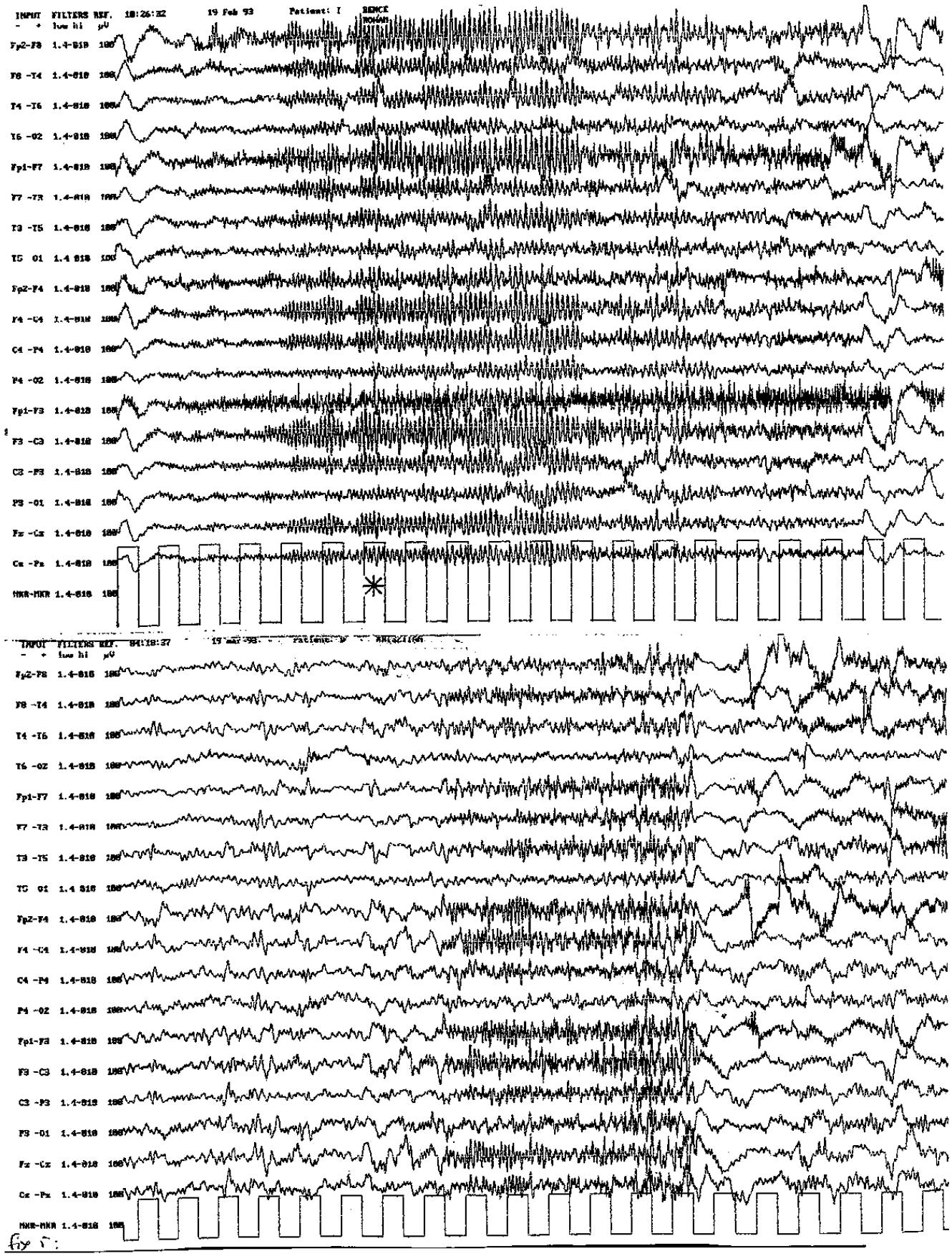
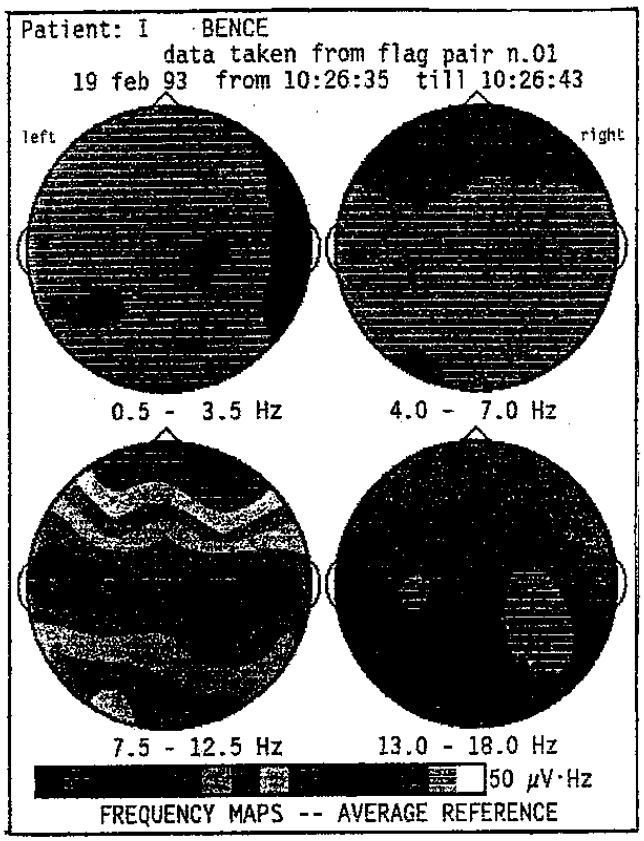
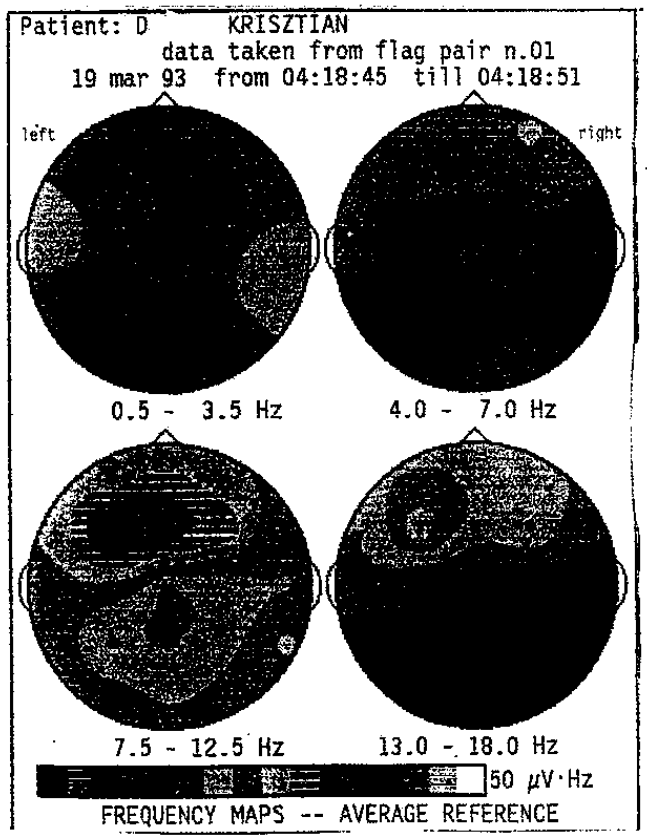


Fig. 5. Two kinds of bifrontal negative fields in the 7.5-12.5 Hz range of power maps during GRFD pattern: a. frontopolar and b. vertex type.





however, it is not always irreversible and may transiently appear under the influence of certain drugs.

MATERIAL and METHODS

All the patients showing GRFD pattern transiently or permanently in the last ten years were incorporated in the study. The data of 29 patients with GRFD were analysed retrospectively. Most of the patients were followed by us (P.H) under personal care from 10 to 30 years. The data of all the patients were analysed by searching and reevaluating the EEG, clinical and neuroimaging records gathered from different institutions treating the patients since the onset of the illness.

GRFDs were detected in more than one records only in 10 patients and among them in 4 cases GRFDs proved to be a transient phenomenon (TRANS group). In 13 patients the GRFD was detected only in a single record either in sleep or in awake state.

In 10 patients the GRFD was pharmacologically tested by i.v. administered diazepam, hexobarbital, and-or flumazenil under video-EEG control. In 7 patients the GRFD pattern was analysed by the power map method.

FINDINGS

Clinical aspects

Our 29 patients including 23 exhibiting GRFD and 6 LRFD at least once in their EEG records were divided into different groups either on the basis of the type of original epilepsy from where the evolution started or the clinical forms in which the GRFD or RFD appeared.

The distribution of the original groups evolving to the later froms with GRFD are shown in fig. 1.

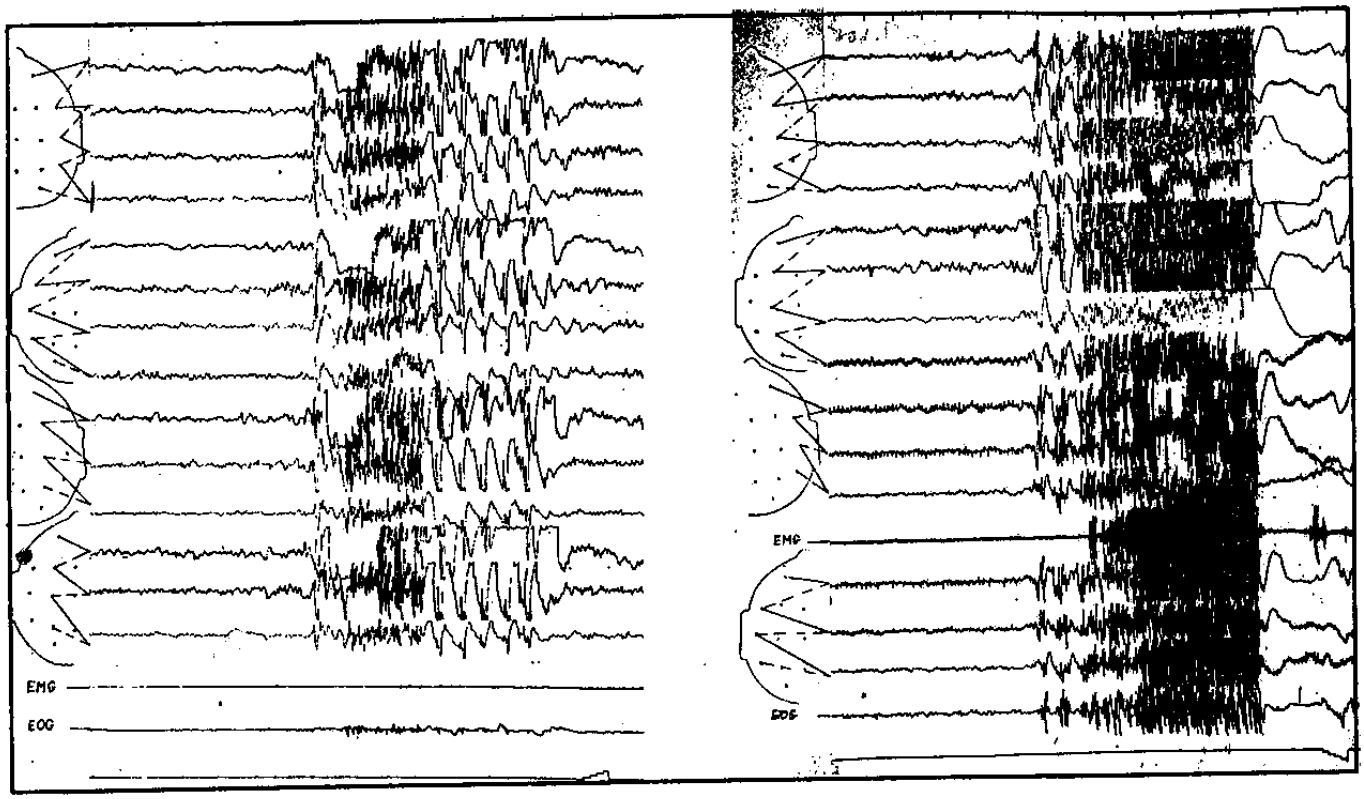


Fig. 6. Transition of spike-wave and GRFD patterns within one episode. Two variations.
a. transition from GRFD to spike-wave and b. from spike-wave to GRFD occuring in the same patient.

Patients in the present stage of evolution were be grouped as follows: 1: Lennox-Gastaut syndrome (LGS): 8 patients, 2: Late Lennox-Gastaut syndrome (LLGS): 5 patients (all of them evolved from generalized epilepsy) 3: Secondary generalized epilepsies (SGEP): 10 patients (the evolution from partial epilepsy was followed personally in 5 patients) 4: Patients showing the pattern only transiently (TRANS), under the influence of certain drug regimes. The clinical characteristics of the patients are shown in table I.

Electrographic characteristics of GRFDs

Morphology and pattern

We observed three kinds of morphological pattern in the GRFDs. Those were: 1. crescendo, 2. decrescendo, and 3. fluctuating spindle shape types. No correlation was found with the other EEG or clinical features, however there was a tendency of the spike waves to appear of the end of the crescendo and in the beginning of the decrescendo type, while the fluctuating spindle shape pattern showed fewer spike-wave components.

Frequency

The frequency of GRFDs varied from 9 to 22 Hz in our patients. The average frequency was 13 Hz (SD: 2.88). The histogram of the frequencies show a tendency for two peaks: one around 10 Hz and the other around 15-16 Hz, but is seems to be a rather continuous transition between these two peaks (fig. 2).

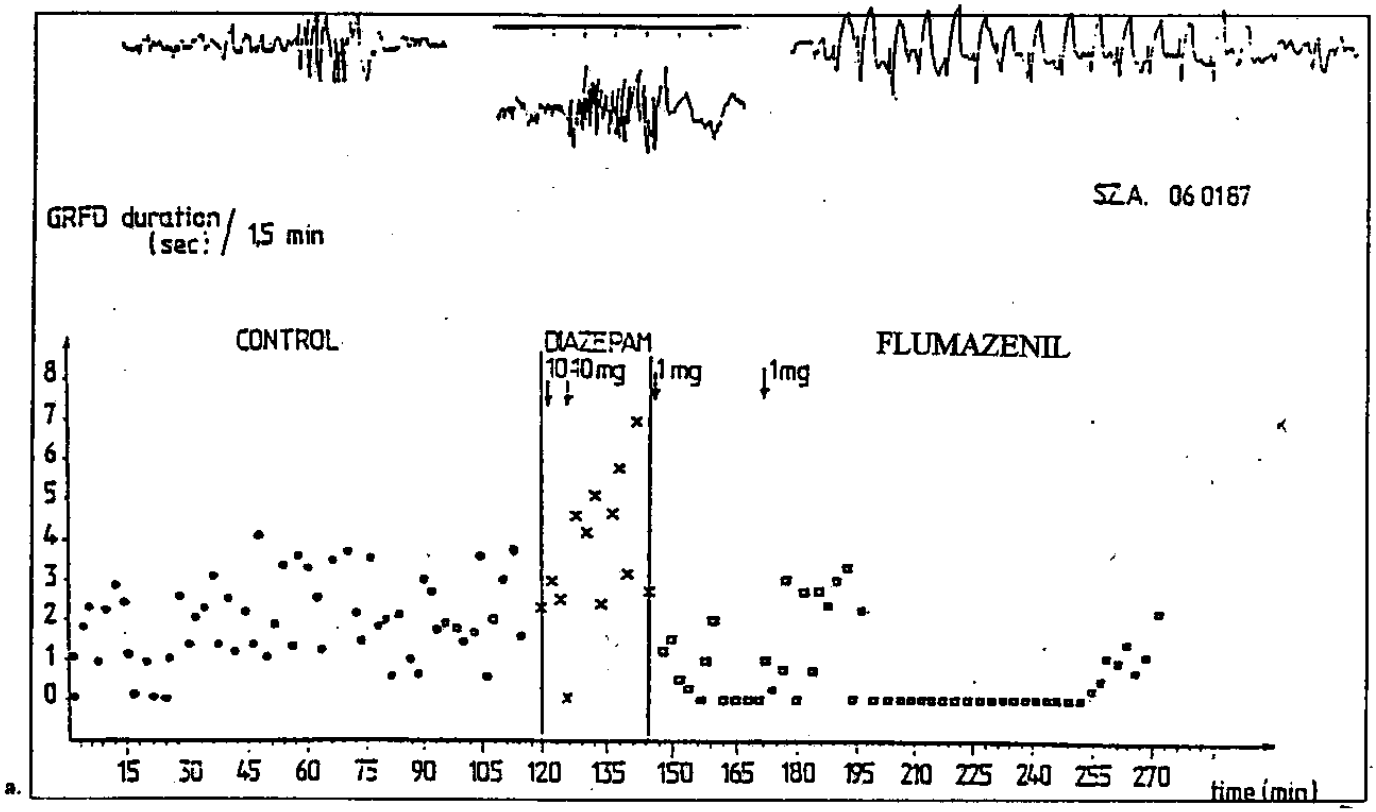
The frequency was the highest in the classic LGS group (average: 14.56 Hz) and the lowest in the PE group (average 11.58 Hz.). Analysing the frequencies according the type of original epilepsies no differences could be detected between those coming from PE and GEs, but both of them proved to be lower than those having LGS from the start (fig. 3). There was a significant correlation between the age of onset epilepsy and the frequency of GRFD: the earlier the onset the higher the frequency was.

Duration

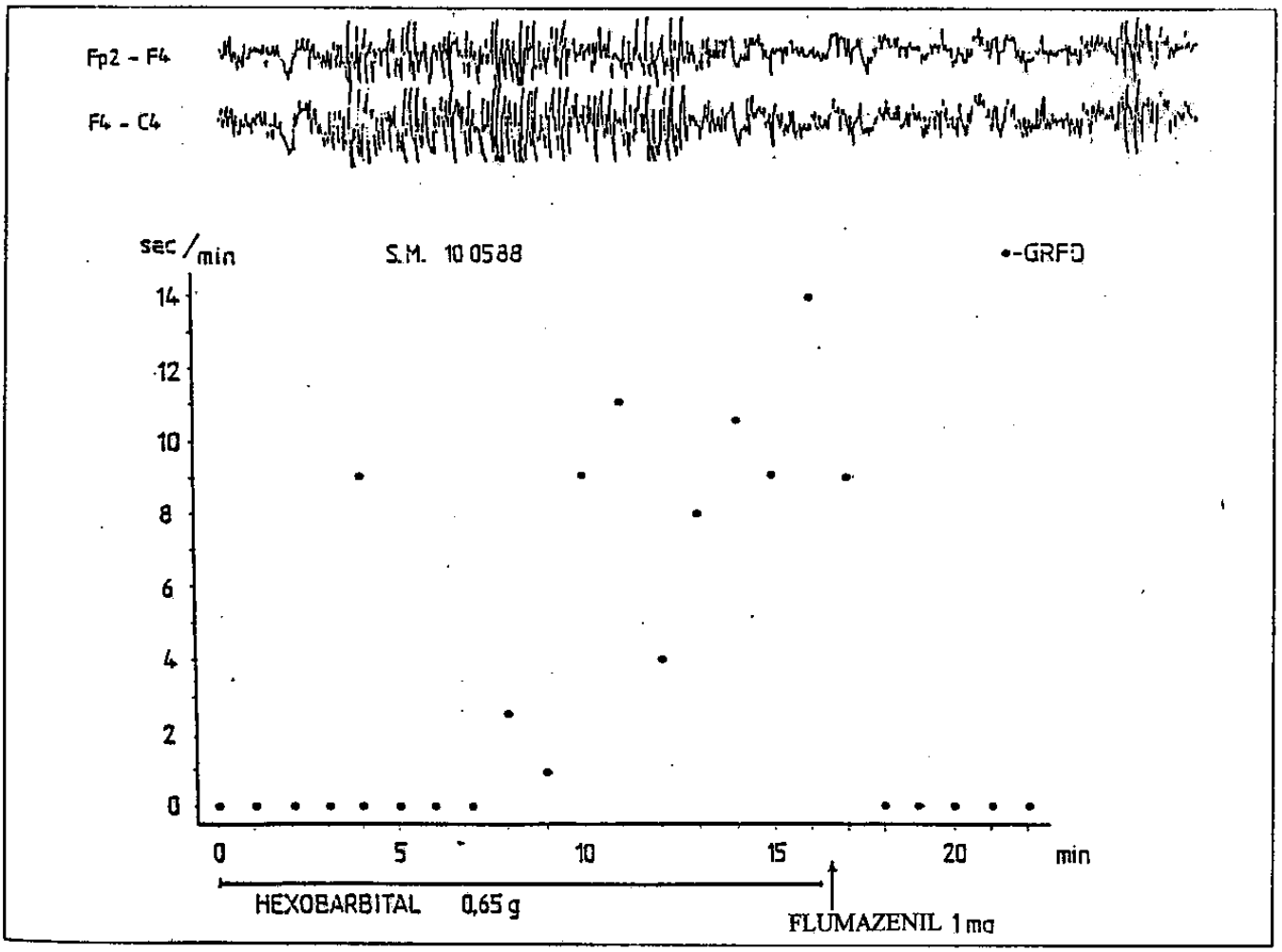
Duration of GRFDs varied from 2 to 18 sec in our patients, and in the majority they were shorter than 13 sec. The duration seems to be shortest in the PE and longest in the LGS group when grouped according to the type of original epilepsy the shortest ones GRFDs those evolving from PE and longer from GE, while longest GRFDs were in patients with LGS originally (fig. 3).

Localization

Investigated either by power or by amplitude map method the GRFD pattern showed large bifrontal negative fields constituting the negative end of dipoles the positive end of which were extending to the posterior regions of the scalp. The axes of these dipoles were situated horizontally. The frontal negative fields were far from being homogeneous, most of them having a bilateral epicenter, but some of them apparently having a midline maximum. Analysis of the single waves of the GRFD pattern performing amplitude maps on different parts-either on the descending and ascending slope or on the peak-of a wave showed, that the frontal maxima to be very often lateralized and mosaic like varience (fig. 4). Two types could be distinguished: one with more frontopolar and one with a vertex maxi-



a.



b.

Fig. 7. a. GRFD activated by Diazepam (10-40 mg), and inactivated by Flumazenil 1 mg twicely notice that spike-wave activity remained untouched, b. GRFD activated by Hexobarbital 0.65 g and inactivated by 1 mg Flumazenil

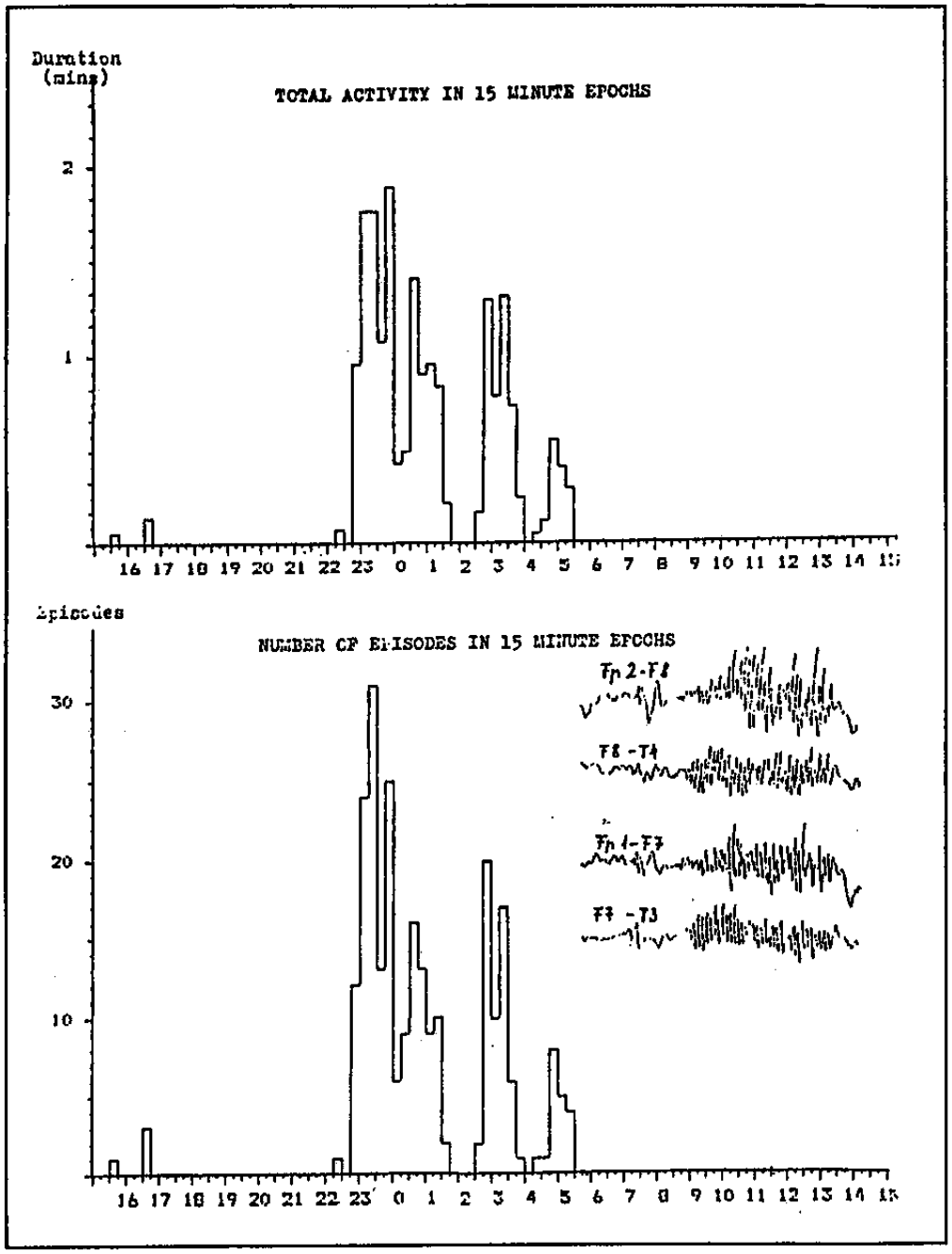


Fig. 8. Distribution of duration (above) and number of epizodes of GRFD pattern during 24 hour.

mum (fig. 5). The number of observations are too few at this moment to look for the correlation of map characteristics with clinical forms. However there is a tendency of relationship between the polar form with LGS and the vertex form with the secondary evolved GRFD types.

Correlation with spike-wave pattern

In all of our patients except 4 generalized spike-wave synchronisation was detected either as a permanent or transiently observed feature regardless the actual presence or absence of GRFD. Appearence of spike-wave complexes before, during or following the GRFD pattern was observed in 12 patients (fig. 6).

Background EEG

In 18 patients the background EEG showed definitive diffuse slowing while in others, it remained preserved.

Pharmacological response

In 10 patients the behaviour of GRFDs was tested by benzodiazepines and by hexobarbital, in some of them several tests were carried out. Seven patients received i.v. diazepam (20-30 mg) in bolus form and in 4 the previously not visible GRFDs appeared or became more frequent and prominent (fig. 7a). This effect was not always asosciated with somnolence or sleep. In 2 patients diazepam did not

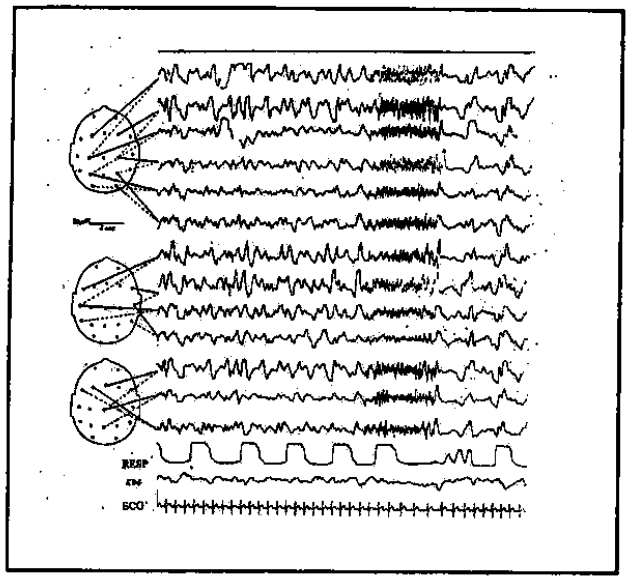


Fig. 9 GRFD in deep slow wave sleep followed by brief post-paroxysmal depression of EEG activity, associated with short apnoe and slowing of heart rate as only ictal manifestations.

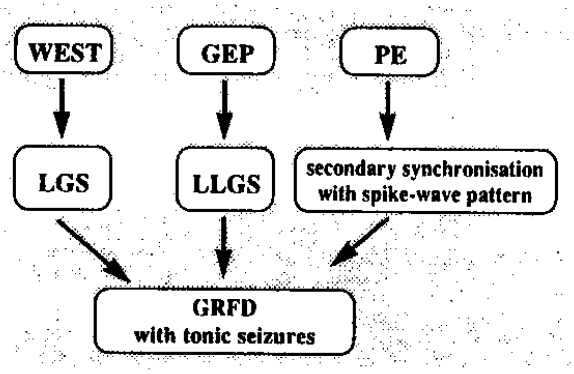


Fig. 10 Routes of malignant evolution from different sources converging towards GRFD with tonic axial seizures as final common condition.

activate the GRFDs however in 1 of them in an other occasion the test was positive during high dose benzodiazepine and phenobarbital administration. All the positive tests were obtained during either benzodiazepine and/or phenobarbital treatment showing high blood level of the drugs.

I.V. Hexobarbital in 4 patients from 6 injected activated the GRFD pattern along with sleepiness (fig. 7b). In the only patient who had intracarotid hexobarbital injection bilateral GRFD activation took place.

Flumazenil (1-2 mg i.v.) had supressing effect on the GRFDs activated either by diazepam or hexobarbital in all 4 cases who underwent trial (fig. 7a-b). Parallel with the supressing effect of the drug, an arousal influence could be observed.

Relationship with sleep

All patients had the GRFD during sleep and 15 showed the pattern in certain occasions during awake state as well. Three of the TRANS group showed the pattern only in sleep. The pattern occured exclusivelly in slow wave sleep. There was no difference in the expression in different stages of slow wave sleep. A histogram illustrating the distribution of GRFD in sleep is given in fig. 8. The duration of GRFDs was generally shorter in awake state.

Relationship with ictal symptoms

In 14 patients no polygraphic and/or video recordings are available to study the ictal symptoms, however they might have TA seizures (see in table I). In some patients autonomic symptoms (heart rate and/or respiration rate acceleration or deceleration) were detected during sleep (fig. 9). In sleep the most frequent tonic motor symptom was opening of the eyes or slight elevation of the head or tonic upward movement of the eyeballs.

DISCUSSION

Clinical framework of GRFD

Except the LGS group in all our patients GRFD or LRFD evolved during a later course of the illness related to a certain evolution of the epileptic syndrome. In GRFD cases, this evolution was characterized by a generalization of the EEG and clinical epileptic symptoms, by mental deterioration and by drug refractory tonic axial seizures. In the TRANS cases the worsening of the clinical picture was not so pronounced. The long term follow up of West-syndrome by Ohtahara [1] clearly showed that in a considerable amount of children an evolution towards LGS develops. Therefore, to a certain extent, LGS could be considered as a result of an evolution; however data regarding a preceeding West-syndrome could be found in only one of our patients.

The GRFD relating to a malignant transformation of the epileptic syndrome originates from 3 sources in our material: 1. childhood LGS persisting in adulthood, 2. generalized epilepsy with spike-wave synchronisation and, 3. partial epilepsy where both spike-wave and GRFD pattern evolved only later in the course (fig. 1). The 4 TRANS patients originated partially from the GEP and partially from the PE group.

Considering our material and other works providing evidences of a common pathway of progressive transformation in different kind of epilepsies, we

Table I.

Name	Start of Seizures	Seizure Type	IQ	Neuroimaging	Neurol. Deficit	Etiology	Progression	Treatment	Epi Syndrome
S.J. (1956)	14	GTC, c.p., TA	SN	?	no	?	yes	PRM-PHT-CZP	r TLE-mirror focus-surgery SGEP
P.A. (1970)	4	IS, myocl.-astat., TA.	DB	?	no	?	yes abs. and TA SEs	PB-tox	BNS-LGS persist
M.G. (1958)	2	GTC, s.p. atonic	DB	e. parietooccip. lesion (1970)	r.hemipar. callosotomised	meningoenceph.	yes	polyth tox	PE-LRFD
Sz. A. (1963)	4	GTC, myocl. absence, TA	DB	CT neg.	callosotom (1987)	?	yes	polyth	LGS persist
F.Zs. (1965)	3 mo	r.hemigen. TA (in sleep)	DB	centro parietooccip. leptomening angiomatosis	no	Sturge-Weber	no	polyth	LGS persist
P.I. (1959)	21	GTC. TA	N	CT neg MRI neg	no	?	?	PHT-PB	SGEP
S.G. (1965)	4	r.hemicl.myocl abs. GTC, TA	D	CT neg	no	?	yes SEs	polyth tox	PE-SGEP
J.J. (1955)	22	c.p.r.adv. atonic	D	CT MRI cerebell. atroph	no	?	yes	polyth (CZP)	l. TLE-bilat TLE-LRFD (l)
B.G. (1942)	17	hypermot. TA (in sleep)	N	CT neg	no	?	?		SGEP
D.K. (1971)	7	r.faciobrach. (in sleep). atonic. GTC	N	CT, MRI neg	no	?	yes	PHT-VPA tox	PE-SGEP
K.Cs. (1973)	9	GTC., TA (in sleep)	DB	CT, MRI neg	no	?	yes	polyth	SGEP
P.Sz. (1971)	12	c.p. GTC, (rare)	N	CT neg MRI MTS. PET: bitemp. hypometabolism	no	local periventriheterotopia (trigonum)	yes	PHT tox	r-TLE-mirror-focus LFRD
S.M. (1946)	15	abs, GTC, TA.	D	CT neg	no, later status post callosotomy	?	yes SEs	PHT-PB-BDZ	GEP-LLGS
H.J. (1951)	10	r.adv.GTC, c.p.	DB	?	no	?	?	CBZ-VPA	LLGS
T.B. (1970)	13	atyp.abs.TA.	DB-IMB	CT, MRI neg	no	?	yes	VPA-SUX	LLGS
L.G. (1976)	9 months	myocl-astat.c.p., TA	DB-IMB	CT neg	no	?	yes	PB-CZP	LGS persist
K.R. (1978)	10	myocl.abs.GTC, atonic	N	CT neg	no	? dysgen?	yes	PB tox	SGEP
N.F. (1961)	12	GTC, atonic, TA.	DB	CT, MRI neg	brain stem nystagmus	?	yes	PRM-CBZ-VPA-BDZ-GLUTETH	SGEP
Cs.J. (1967)	2	TA. (in sleep later in awake)	DB-D	?	no	?	yes	PRIM	LGS persist
I.B. (1944)	3	GTC, TA.	N-D	CT mild cort. atroph	no	?	yes	PHT-PB	LGS persist
M.R. (1976)	5	EPC(r), myocl-astat. ton (l)	D	CT MRI serious l. hemisph damage	r.hemi-sy	Rassmussen enceph.	yes	PHT-PRM CZP tox	PE-LRFD
E.G. (1976)	3.5	myocl-astat. GTC, TA.	DB-IMB	CT neg	ataxia	?	yes ESs	polyth	LGS
N.L. (1953)	8	atyp.abs.GTC, atonic, TA.	SN	CT MRI cerebell atr sec l. front. damage	ataxia	?	yes	PHT tox	GEP-LLGS
F.F. (1961)	9	myocl. abs, GTC, TA.	N	CT: r. ventr dilat r. hyp odens lesion	no	?	yes	PB, BDZ, PHT, PRM tox	GEP-LLGS
M.D. (1982)	2	c.p.rare GTC	N	CT MRI: l. temp. lesion (tu)	no	ganglio-glioma	yes	CBZ, BDZ	TLE-LRFD
T.T. (1964)	5	myocl-astat., TA, rare GTC	DB-D	CT neg	no	?	yes	polyth	LGS persist
M.S. (1968)	8	TA	DB	CT neg	no	?	yes	CBZ-VPA BDZ	PE-SGEP
N.T. (1966)	14	GTC	N	CT neg	no	?	yes	PHT-PRM SULTH	PE-SGEP
T.I. (1949)	12	GTC, l. adv. c.p.	D	CT, MR neg	no	?	yes	PHT-CBZ PB	SGEP

Abbreviations:
abs.-absence; **adv**-adversion; **atyp**-atypical; **bilat**-bilateral; **BDZ**-benzodiazepine; **c.p.**-complex partial seizures; **CZP**-carbamazepine; **CLON**-clonazepam; **D**-demented; **DB**-debil; **EPC**-epilepsia partialis continua; **faciobrach.**-faciobrachial seizure; **GLUTETH**-glutethimid; **GTC**-generalised tonic clonic seizure; **hypermot**-hypermotor seizure; **IMB**-imbecile; **IS**-infantile spasm; **l**-left; **myocl.-astat.**-myoclonic-astatic seizure; **N**-normal; **PB**-phenobarbital; **PHT**-phenytoin; **polyth**-polytherapy; **PRM**-primidone; **r**-right; **s.p.**-simple partial seizure; **SE**-status epilepticus; **SN**-subnormal; **TA**-tonic axial seizure; **ton**-tonic seizure; **tox**-toxic state; **VPA**-valproate

propose a schema of evolution (fig. 10) where GRFD associated with tonic axial seizures represents a possible common endstation.

GRFDs as a distinct and meaningful EEG pattern

This type of EEG manifestation was first recognized by Jasper and Kershman [2] who called it "paroxysmal fast rhythm". Later the pattern was designated by different names given by different workers [3] "grand mal type of discharge", Gastaut [4]: "epileptic recruiting rhythm", Niedermeyer [5]: "runs of rapid spikes", Brenner and Atkinson [6]: "generalized paroxysmal fast activity".

In this paper we shall use our own term: "generalized repetitive fast discharges (GRFD)" [7] being above all descriptive, without any connotation.

The pattern consists of bursts of generalized rhythmic rapid discharges the frequency of which ranges from 8 to 26 Hz. Two groups could be distinguished [8]: one around 12-4 Hz and another around 22-4 Hz. The duration is variable within range from 2 to 40-50 sec, in sleep, usually under 10 sec. In the latter half of the discharges slow waves may interrupt the fast discharges and are frequently followed by slow waves and or by transitory postparoxysmal depression of the activiy.

In the last two decades GRFD was related to Lennox-Gastaut syndrome (LGS) as an essential feature of the syndrome [9], either in classic childhood form or in the later recognized postpubertal (late LGS-LLGS) variant [10-13]. Besides this classic association of the pattern with LGS, random observations appeared showing the manifestation of GRFD associated with evolutive forms of partial-mainly frontal and temporal-epilepsies [14,15].

All the publications are in agreement that the occurence of GRFD could be assumed as an indicator of drug refractory seizures of probable bad prognosis and also of the likelihood of mental deterioration.

Relationship with the spike-wave pattern

It is a trivial condition for LGS and LLGS that GRFDs are present in addition to the slow spike-waves. The same seems to be true for the group where GRFD evolves after a previous history of partial epilepsy. In these cases a secondary synchronisation in the form of bilateral spike-wave pattern developes before or at the same time with the GRFDs. The close relationship with the spike-wave pattern was stressed already by some earlier works [3,16,17].

Several arguments could be proposed supporting a close relationship between GRFDs and spike-waves. Rich variations of different mixtures of the two patterns could be seen in the ictal discharges, and a morphological continuum of the patterns extending from the spike-wave to GRFD with intermediary forms where spike-waves begin, adjacent to or mixed up with GRFDs could be observed. The distribution over the scalp measured by the power map technic is quite similar: both type of discharges show a frontal predominance. The propensity for appearence of both kind of discharges is enhanced both by slow wave sleep and sleep induced by Hexobarbital. The corpus callosum plays an important role in the organizaton (synchronisation) of both patterns as it was demonstrated in our callosotomised case.

The assumption that the differences between spike-waves and GRFDs could stem mainly from differences between the role of inhibitory mechanisms could be supported by the presence of postictal exhaustion signs after GRFDs and a lack of them following the spike-wave discharge. The differences in the seizure symptoms in conjunction with these two patterns, namely tonic axial motor seizures with GRFDs and no motor symptom or only myoclonic jerks, with the spike-waves are in good agreement with the role of inhibition as a cause of difference between these two patterns.

Taking into consideration the above mentioned features there is a possibility that GRFD is a derivative of the spike-wave pattern, expressing the breakdown of inhibition reflected in the wave component of the spike-wave pattern [18].

GRFD and neurochemical influences

A large amount of data have been obtained about the

effect of BDZ compounds on the spike-wave pattern and the GRFDs. Spike-wave activity and also GRFD discharges could be supressed by i.v. administered BDZ compounds even if present in the form of status epilepticus [19]. However since the early seventies several publications have appeared describing paradoxical precipitation of the GRFD by BDZ drugs in some patients. Precipitation of tonic status epilepticus with GRFD has been reported in 7 patients with LGS [20-24]. Others have described a transient increase of GRFDs immediately after the injection of diazepam or clonazepam [25,26]. Japanese workers have reported about induced GRFDs (microseizures) in West-syndrome under chronic clonazepam treatment disappearing after cessation of clonazepam [27]. The multiplication of spike components as a shift towards GRFD was observed in patients with generalized epilepsy under chronic diazepam treatment in small doses while larger i.v. doses still exerted a strong anticonvulsive effect [28,29].

In a smaller group of our patients the GRFD pattern could be detected only for a short time as a new variation in the EEG follow ups, probably under the influence of certain drug or drugs. The influence of certain drugs-most probable phenobarbital and or benzodiazepines-verified by the disappearence of the pattern after withdrawal of these drugs and by the activation of the pattern with hexobarbital and diazepam antagonized by flumazenil, raise up the possibility that this type of malignant transition could be developed by a certain long term influence on the postsynaptic receptors. The most likely candidate as a substrate of this change is the chloridionophor GABA. A-barbiturate-benzodiazepine receptor complex. This receptor complex is known to have a shift from agonist towards inverse agonist position under the influence of chronic benzodiazepine effect [30,31]. It is questionable whether such response to these drugs indicates the presence of an earlier-occult- change in the receptor structure which would be the substrate of the malignisation process. The other possibility is that this malignant receptor constellation did not exist previously but was introduced just under the influence of the drugs making certain changes in the receptor structure, being reversible and drug-dependent. Besides this possibility it might be assumed that this kind of malignisaton or malignant disorder developes without external drug influence in the LGS condition. In other words, a similar kind of change in the complex receptor structure, responsible of neuronal inhibition could be the substrate of the malignant features, as tonic seizures and GRFD which could be promoted by PB and BDZ drugs in patients inclined to develope the same malignant symptomes.

We do not know the outcome of these patients at this moment. It is possible that the occurence of the pattern heralds a certain inclination toward this type of malignisation, but the follow up time and the number of patients yet, are not available to confirm this assumption.

Is GRFD assigning a possible common route of malignisation for different kind of epilepsies?

The presence of the pattern in the LGS group needs no special comment hence it belongs per definitionem to the syndrome. The same is true for LLGS. According to the hitherto published papers some cases of LLGS origin from the persistence of LGS in the adulthood, while others follow questionable idiopathic generalized epilepsy. A third group has local, usually temporal or frontal epileptogenic features [11,13,32]. All the three variations could be recognized in our material, however the GRFD in epilepsies showing earlier partial epileptic characteristics, appeared only after a considerable time of evolution. Therefore it is debatable whether this group could be considered as LLGS or it should be treated as a different group characterized by a malignisation of certain partial epilepsies. There are different publications about similar cases having partial epilepsy and characteristics of LGS-like symptomes latter [14, 15].

The evolution of GRFD is a rather rare complication among epilepsies. The pattern was found in 21 records of 20 patients among 7378 EEG records over a 5.5 year period at a university-county hospital of Albuquerque, excluding the LGS patients [6]. Similar incidence was found by the Gibbses in the early fourties [33]. Our material was accumulated over 10 years in an epilepsy center dealing mainly with severe epileptic patients.

The progressive nature of certain epilepsies is well-known for a long time, while the benign course of

others became clear in the last decades. The mechanisms by which an epileptic disorder could progress were studied and explored as propagation or secondary epileptogenesis and generalization or more properly secondary generalization [34].

We propose here another type of mechanism playing a possible role in the progression of epilepsies on a wide scale. This is the malignisation through loss of local inhibition or breakdown of inhibition as a second step after propagation in the form of secondary bilateral spike-wave synchronisation. We named this type of malignisation as Lennoxisation.

There is a knowledge that, in certain epileptic mechanisms, inhibition is preserved or even enhanced [35]. Generalized epilepsies and hippocampal regional epileptic disorders behave in such manner [36] exhibiting spike-wake like EEG expression while other epileptic mechanisms where the inhibition is not enhanced or possibly not even preserved behave as a more malignant variant and expressed by low voltage fast ictal activity without intermingled slow waves. GRFD seems to be a condition were a shift is accomplished in the nature of the epileptic disorder from the initial towards the latter type of mechanism.

The physiopathogenesis of secondary synchronisation, that is the evolvement of secondary bilateral spike-wave pattern, is one of the great unraveled enigmas in the history of EEG and epileptology. Earlier workers addressed this question in several papers [37,38] but recently few papers [34,39] dealed with this topic. It became more or less clear that the projection theory assuming that the persistence of a local epileptogenic area in certain localizations induce changes in the non specific thalamic structures projecting the disorder in the form of generalized spike-wave pattern over widespread cortical areas, could not be proved. At the same time the generalized form of the spike wave discharges also became questionable under the more scrutinized investigations done by measuring the interhemispheric differences in the discharges [40] and by the mapping studies [41,42]. Consequently a part of the bilateral slow spike-wave patterns should be held as the result of contralateral spread of spike-wave discharges coming from a wide area of the ipsilateral hemisphere. However studies after callosotomies showed that the propensity of spike-wave formation could remain preserved independently over both of the dissected hemispheres [38]. The conception of Gloor and Fariello [43] helped to consider the question in a different way. Not the projection of the epileptiform discharges but the epileptic facilitation of the cortex receiving the physiological impulses from the non-specific thalamic system results the spike-wave formation, and differences in the epileptic facilitation could make local enhancements while the interhemispheric synchronisation is carried out through the corpus callosum.

If we accept that the malignisation in the form of GRFD is a second step after the evolvement of spike-wave synchronisation wide variation of epilepsies where the involvement of the thalamic non-specific system develop are possible candidates for this kind of progression.

GRFD should be considered as an indicator of this type of malignisation (Lennoxisation), however at the moment of observation still in a beginning and reversible form. The malignisation process usually evolves as a second step after the evolution of secondary synchronisation in the form of generalized slow spike-wave pattern by the loss of inhibition over the cortical area of the original irritative zone (local forms), or widely over the cortex (generalized forms). In some of our patients the spike-wave generalization could not be detected, but the follow up of the these patients was not long enough, so it is possible that they might have had the pattern for a limited period of time.

The localized development of the repetitive fast discharge could raise up interesting physiopathogenetic considerations. This fact shows that the essential components of GRFD are concerned with the local cortical network, and not with the non-specific projection systems. The findings of Palmini et al [44] who observed similar local EEG pattern in cases of cortical dysplasias point to the same direction.

Some of our patients showed more benign features compared with the bulk majority. In a all of them the pattern was observed only transitorily. Miller and Ferrendelli reported two neurologically normal pa-

tients who had eyelid twitching seizures with GRFD pattern [45]. There is no information whether GRFD was present for a long time in their EEG records or was it a new feature.

At present we do not know whether there exists a benign variation of epilepsy with GRFDs or if those cases present an initial phase of progression.

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