The pathophysiology of Lennox-Gastaut syndrome – a review of clinico-electrophysiological studies

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SUMMARY

Introduction. Lennox-Gastaut syndrome (LGS) is a type of therapy-resistant epileptic syndrome. Since the establishment of our Epilepsy Center in 1975 we have performed many studies to assess the clinical symptoms, seizure manifestations, sleep and long-term follow-up of the clinical course and changes on electroencephalographs (EEGs) in patients with LGS.

Aim. To review the updated pathophysiology of LGS based on our own clinico-electrophysiological data referring to recent advances in brain research.

Methods. All of our previously published and unpublished data were reviewed in order to investigate the pathophysiology of LGS and using PubMed database for relevant literature.

Results and Discussion. While LGS usually occurs in infancy, it has become apparent that there is a form of late-onset LGS (L-LGS) that may occur at age eight or older. L-LGS often occurs when there is a history of encephalitis/encephalopathy or status epilepticus. The long-term progression of LGS includes mainly tonic seizures that persist and are the basis of LGS. In approximately 30% of cases, the basic symptoms of LGS remain 10 years or longer after long-term progression, while the rest lose their characteristics, although the condition is residual in 60% of cases and remission occurs in fewer than 10%. Among the characteristic seizures associated with LGS, atypical absence seizures occur in response to a diverse range of EEG features; wherein, while they are mostly short, they are accompanied by a state of enervation along with a tendency for it to be unclear when the seizure has ended. Drop attacks can in fact be categorized into those in which the subject falls over due to hypertonia in the muscles used to maintain body posture and those in which the subject falls over due to loss of tension in the posture-retaining muscles. Tonic seizures range from those manifesting in the form of extremely mild axial muscle tonicity, open eyes and respiratory changes, accompanied by high voltage, fast rhythm (averaging 14 ± 0.4 Hz), or tonicity from axorhyzomelic muscles to the peripheral muscles, accompanying global tonic seizures, and EEG features showing low voltage fast activity (averaging 22 ± 0.6 Hz) from desynchronization. A total of 1191 clinical seizures were recorded upon overnight polysomnography and videotape, and seizure symptoms and their ictal EEGs were analyzed. In LGS, seizure activity increases during slow wave sleep, inhibiting progression into the further sleep stages but falls significantly during rapid eye movement (REM) sleep.

Conclusions. From the research into seizure symptoms, clinical progression, sleep and seizures during sleep, it was believed that in LGS epileptic native lesions occur due to mesencephalic reticular formation, in the thalamic reticular system and, as a result of recent of brain physiology research, it is considered that LGS is an epileptic reticulo-thalamo-cortical system disorder. This has been supported by EEG-fMRI findings (Siniatchikin et al., 2011). Further research is therefore necessary to elucidate the role of the reticular formation in controlling the thalamo-cortical networks in humans.

Key words: Lennox-Gastaut syndrome • clinico-encephalographic studies • long-term follow-up • tonic seizure • pathophysiology • epileptic reticulo-thalamo-cortical system disorder

INTRODUCTION

Lennox-Gastaut syndrome (LGS) is a generally recognized, almost incurable type of epilepsy (Crespel et al., 2012). In a study undertaken for the purpose of proposing a classification system for epilepsy in 1989, in which 300 patients hospitalized in the Epilepsy Center who experienced a minimum of one or more seizures per month upon discharge, showed that 68 cases (22.7%) were LGS (Yagi and Seino, 1989). The natural conclusion was a desire to truly understand the condition of LGS. Since the establishment of our Epilepsy Center in 1975 we have performed many studies to assess the clinical symptoms, seizure manifestations, sleep and long-term follow-up of the clinical course and changes on electroencephalograms (EEGs) in patients with LGS.

AIM

To consider the updated pathophysiology of LGS based on our own clinico-electrophysiological data referring to recent advances in brain research.

METHODS

All of our previously published and unpublished data were reviewed in order to investigate the pathophysiology of LGS. The data are presented as follows:

1. Analysis of adult LGS.
2. LGS progression – long-term, longitudinal research.
3. Pathophysiological researches into LGS.
4. Generalizations related to LGS, along with observations regarding the epileptogenic mechanism.

The authors wish to reconsider the pathophysiology of LGS by reviewing the research that has been conducted to date using the PubMed database.

RESULTS AND DISUCSSION

1. Analysis of adult LGS (Yagi et al., 1983)

LGS has already been reported by various researchers to be an age-dependent epileptic encephalopathy, with onset in childhood, and has been extensively researched in the world (Gastaut et al., 1966; Kruse, 1968; Schneider et al., 1970; Chevrie and Aicardi, 1972; Blume et al., 1973; Ohtahara et al., 1976). Around the same time, Gastaut et al. (1966) and Lipinski (1977) reported that it could also begin in adolescence or adulthood. Each of these reports referenced to only a small number of cases, with the characteristics of the syndrome in adulthood not clear.

For this reason, the authors studied an adult group, comprising 70 patients hospitalized with LGS aged 20 or older, along with a control group for comparison, comprising 103 patients with LGS aged 15 or younger, and compared the age at which epilepsy onset, the age at which the patients were diagnosed to have LGS, their medical history and their pathology. The results of this study showed that the average age of epilepsy onset in the adult group was 11.3 ± 4.9 years, while in the comparison group it was 2.6 ± 2 years. The average age of diagnosed adult group was 16.9 ± 5.9 and 4.5 ± 2.8 years of comparison group. While the medical history (Table 1) showed no significant difference in positive test results between the groups (49% and 48%), the adult group had a greater history of encephalitis or encephalopathy (22.8% compared with 10.7%). Although the control group had a higher proportion of perinatal injury (27.2%, compared with 14.3% in the adult group), there was no difference between the two groups with regard to their history of external injury, and while the control group had slightly higher incidence of congenital abnormalities such as tuberous sclerosis, the adult

Table 1. Comparison of past history between an adult group with Lennox-Gastaut syndrome and a control group

Past History	Adult group (N = 70)	Control group (N = 103)
Negative	34 (49.0%)	54 (52.0%)
Positive	36 (51.0%)	49 (48.0%)
Encephalitis /encephalopathy	16 (22.8%)	11 (10.7%)
Perinatal brain damage	10 (14.3%)	28 (27.2%)
Convulsive status epilepticus	20 (28.5%)	7 (6.8%)
Head trauma	4 (5.7%)	3 (2.9%)
Others(tuberous sclerosis, vascular anomaly, etc.)	3 (4.2%)	10 (9.7%)
West →LGS	1 (1.4%)	24 (23.3%)
Disposition	3 (4.2%)	2 (1.9%)
Psychotic problems	10 (14.3%)	0

group had a significantly higher rate of convulsive status epilepticus (28.5%, compared with 6.8%). A transition from West syndrome was seen in one case in the adult group (1.4%) but a far higher proportion was observed in the comparison group (23.3%). Within the adult group, there were 10 cases (14.3%) in which the patient had been hospitalized in a psychiatric hospital for abnormal behavior or psychiatric symptoms. In terms of mental disability, 10% of the 70 cases in the adult group were above the boundary, 80% had mild or medium disabilities and a further 10% had severe disabilities. The type of seizures that occurred while admitted to hospital were tonic seizures in 94% of cases, atypical absence in 81%, atonic seizure in 59%, tonic-clonic seizure in 17%, myoclonic seizure in 6% and partial seizure in 16%.

EEG revealed background activity between 8–11 Hz α-activity in 46% of the adult group, with θ-activity slower than 8 Hz in 52%. A pseudo-rhythmic slow spike-and-wave complexes was seen in all cases, with a run of rapid spikes in 61 out of 70 cases (87%).

Of the 60 cases that had a CT scan. 12 (20%) were normal and 48 cases (80%) had some abnormality; 42 of which demonstrated generalized cerebral atrophy. While seizures were controlled in three of the 70 cases, the others were resistant to treatment and essentially incurable.

When the 70 adult LGS patients were categorized according to the age at which their epilepsy onset, with onset under the age of eight (most cases occur under the age of 6) classified as "early" and onset at age eight or above classified as "late", 20 cases were early and 50 were late. As has been already discussed, 23% of the adult group had a history of encephalitis or encephalopathy, with 29% having a history of status epilepticus and 80% having abnormalities in CT scans. It can be assumed from this that the cerebrum itself sustained some damage and that frequent epileptic attacks have contributed to worsening of the condition.

2. LGS progression-long-term, longitudinal research (Yagi, 1996)

At our Epilepsy Center, we often saw patients with fully developed LGS and it was rare to be able to follow a case of infant epilepsy from onset and observe it over time. For this reason, we studied the progression of 102 LGS cases in which follow-up was possible over 10 years or more (82 of these had been hospitalized once or more). The average age during the survey was 28.6 years (15–69 years), the average of epilepsy onset 4.3 years (1 year 3 months–43 years) and the average length of the follow-up period 16.3 years (10–20 years).

Types of seizure experienced at the time of the survey

Of the 102 patients surveyed (Table 2), eight had not experienced attacks for one year or longer, with the remaining 94 subjects to attacks, of which 91 (96.8%) had tonic seizures. In 52 of these 91 cases, the patients experienced tonic seizures alone and in 17 of these 52 cases tonic seizures were experienced only at night. Furthermore, 11 cases experienced tonic seizures + absence seizures + drop attacks (one of which also had partial seizures), 13 cases experienced tonic seizures + absence seizures (of which one also had myoclonic seizures and one partial seizures), 12 cases experienced tonic seizures + drop attacks (of which one also had myoclonic

Table 2. Type of seizures at the survey in 102 Lennox-Gastaut syndrome patients

Type of seizures	Number of seizures
Tonic seizure	52 (17 in sleep)
Tonic, absence, astatic	10
Tonic, absence	11
Tonic, astatic	11
Tonic, myoclonic	3
Tonic, absence, myoclonic	1
Tonic, astatic, myoclonic	1
Tonic, absence, astatic, partial	1
Tonic, absence, partial	1
Myoclonic	3
Seizure free	8

Tonic seizures persist in 91 of 102 patients with LGS, 88.2% for more than 10 years.

seizures), three cases experienced tonic seizure + myoclonic seizures, and three cases experienced myoclonic seizures alone. None of the 102 cases had only partial seizures as their residual condition.

In conclusion, tonic seizures are a type of seizure that continues over the long term in LGS cases and are considered to be the fundamental seizure of LGS. LGS is a form of epilepsy that manly involves tonic seizures and can be accompanied by absence seizures, drop attacks (astatic seizures), myoclonic attacks, etc.

Progression of epilepsy

When the 102 cases were retrospectively considered in terms of the progress in LGS, the results showed that 44 cases were diagnosed as LGS from the start, 22 had transitioned from West syndrome and the remaining 36 had transitioned from epilepsy determined as neither general nor partial (unspecified epilepsies) to LGS.

Upon examination at the time of the survey, which was 10 years or more after being diagnosed with LGS at our Center, while 33 cases still demonstrated characteristics of LGS, 64 no longer met the criteria and were in a state that could be called progressive or residual, with only eight cases in which seizures had been controlled, resulting in them being in a state of remission.

Changes in epileptic ictal discharge (Yagi, 1990; 1996)

Follow-up was performed annually on the EEGs of the 102 cases, such that a minimum of 10 and maximum of 79 records were created for each case. In all cases, a record was taken from wakefulness through to sleep. Analysis of EEGs looked at slow spike-and-wave complexes, fast rhythm, localized sharp wave and spikes. Fast rhythm was defined as anything continuing for 0.5 seconds or longer, while anything shorter than this was included in multiple spikes. There was no particular reason for dividing the two at 0.5 seconds; this was entirely subjective. Localized spikes and sharp waves were included if they were locally present in the same location for a period of two years or more. Disappearance of epileptic discharges was only included if it was confirmed via EEG for two years or longer. Interpretation of the EEGs was undertaken entirely by the author using the same set of criteria.

In all, 33 cases demonstrated EEGs unique to LGS, such as slow spike-and-wave complexes, fast rhythm and repeated or clustered multiple spikes, continuing for 10 years or longer, while 39 cases showed continual loss of slow spike-and-wave complexes, fast rhythm and repeated or clustered multiple spikes, nine cases had slow spike-and-wave complexes, loss of fast rhythm and residual repeated or clustered multiple spikes, eight had only individually-occurring multiple spikes remaining, three had only residual slow spike-and-wave complexes, one had residual slow spike-and-wave complexes and multiple spikes-and-wave complexes, four had focal spikes in either fast rhythm or slow spike-and-wave complexes, or a combination of the two, and five experienced a loss of abnormal epileptic discharges. In 33% of cases, while no change was observed in the slow spike-and-wave complexes, fast rhythm and repeated or clustered multiple spikes, progress was seen in which slow spike-and-wave complexes, fast rhythm or both either disappeared, or turned into repeated or clustered multiple spike-and-wave complexes, and eventually into single multiple spike-and-wave complexes, before disappearing. There were few cases of residual localized spikes.

Long-term observation of EEG abnormalities showed a process in which generalized abnormal discharges gradually disappeared as it progressed. This confirmed that EEGs also reflect the progress of generalized epilepsy.

Social status at the time of the survey (Yagi, 1996)

Of the 102 cases, five were students at special support schools, while of the remaining 97, 12 were employed and kept working regular hours, one was a housewife, seven had part-time jobs, 19 were cared for at home, 29 worked at vocational or work centers, 21 were residents in care facilities, six were in hospital for treatment of their seizures and the remaining two had died. Of the 12 in regular employment, five had no more than one seizure per year and four had tonic seizures only at night. Two were subject to myoclonic seizure and absence seizures, while one was subject only to myoclonic seizure. Reducing these seizures is important in improving the quality of patients' lives.

3. Pathophysiological researches into LGS

Research into absence seizures (Yagi et al., 1980; 1982)

The absence seizures recorded in simultaneous video-EEG recordings were categorized into typical absence or atypical absence seizures, according to international classification and analyzed by repeated viewing of the videos. A total of 492 absence seizures were recorded from 143 cases, which were categorized into 217 typical absences and 275 atypical absence seizures, from

63 cases and 80 cases, respectively. The age of patients recorded ranged from 5.1 to 35 years for those experiencing typical absence and from 1.4 to 39 years for those experiencing atypical absence seizures. EEG features were 3 Hz spike-and-wave complexes in the case of typical absence and diverse in atypical absence seizures, with a minimum of the following three types: 1) bilateral slightly synchronous, poorly rhythmical approximately 2 Hz slow spike-and-wave complexes; 2) slow spike-and-wave complexes mixed with high voltage fast rhythm (10–12 Hz); or 3) very occasionally, approximately 20 Hz fast rhythm, mixed with slow spike-and-wave complexes (Figure 1). While not seen in idiopathic generalized epilepsy, this type of atypical absence seizure is frequently seen in LGS.

The length of ictal discharge during absence seizures

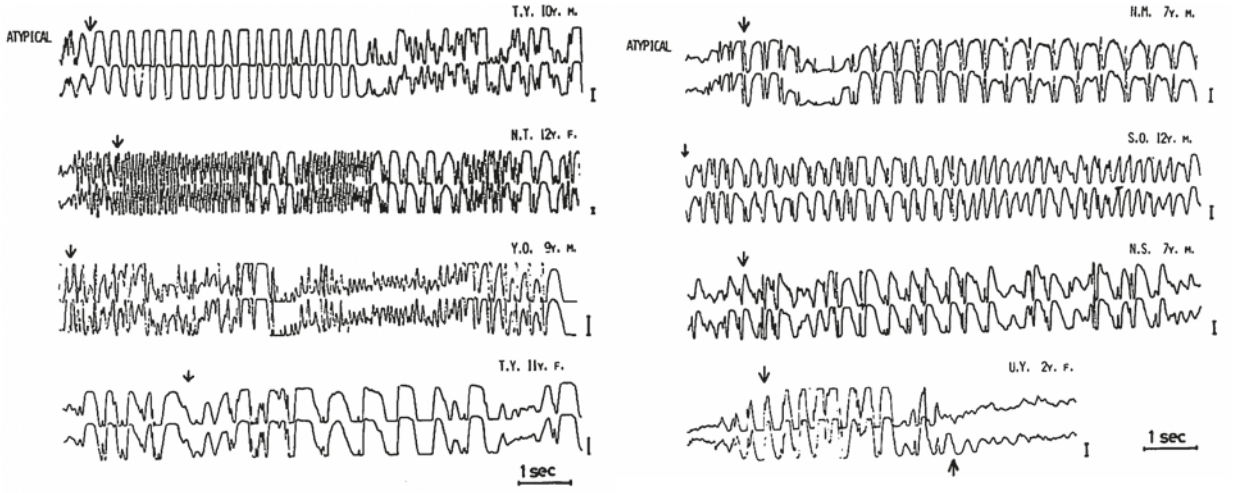


Figure 1. Electroencephalograph diversity during atypical absence seizures (modified from Yagi et al.,1982). Frontal referential leads during seizures in 8 Lennox-Gastaut syndrome patients. The right side bar of each record shows 100 μV Downward arrows indicate the onset of absence seizure manifestation and the upward arrow shows the end of the seizure.

was compared in atypical absence seizures and typical absences, respectively, revealing that 39% and 22% completed within five seconds, while 10% and 0.5%, respectively carried on for longer than 30 seconds, with atypical absence seizures being notably shorter, although the length of discharge was more diverse than that during typical absence. In typical absence, it was completed in 20 seconds or less in approximately 90% of cases.

If attacks in which the ictal discharge along with the start and end of seizure symptoms can be objectively confirmed are studied, and the start and end of ictal discharge in the electroencephalogram is compared with the start and end of clinical symptoms, it is clear that clinical symptoms begin within two seconds of the start of ictal discharge in 88% of atypical absence seizures and in 81% of typical absences. In a very small minority of cases, clinical symptoms were noted prior to discharge beginning, with no difference between the two groups. In all, 78% of atypical absence seizures and 88% of typical absences ended within two seconds of the discharge completing. In 14% of atypical absence seizures and 7% of typical absences, clinical symptoms were eliminated prior to ictal discharge ending. This indicates that the end of an atypical absence seizure is not entirely clear.

We classified atypical absence seizures and typical absence into simple and complex types, according to their accompanying symptoms. Simple absence seizures were defined as those in which no accompanying symptoms occur during the attack, making up 20% of atypical absence seizures and 10% of typical absences. Consequently, 80% and 90% were complex absence, accompanied by some form of accompanying symptoms. These accompanying symptoms were, in a comparison between atypical absence seizures and typical absences, automatism in 32% and 75% of cases, respectively (significantly more common in typical absence), and reduction in tension in posture retaining muscles in 35% and 13% of cases (significantly more common in atypical absences).

To summarize the results above, atypical absence seizures generally have the following attributes: there is a disparity in the length of attacks, with some finishing in a short time but some continuing for 30 seconds or longer, their end is indistinct, they are accompanied by a reduction in tension in posture-retaining muscles; the ictal discharges is a slow spike-and-wave complexes; and they display diversity in terms of a mixture of low voltage fast waves and high voltage fast waves.

Research into tonic seizures (Yagi et al., 1977; 1978)

Tonic seizures frequently occur in LGS patients while they are asleep. The author's analyzed 42 attacks, occurring in 23 patients, recorded using simultaneous recording of EEG during an attack. Analysis was performed to determine the time between the EEG showing early continual spikes and the start of ictal discharge to the occurrence of the attack itself, along with the strength of the attack.

Group in which mild clinical attacks manifested alongside high-voltage spike discharge

In 15 of the 42 attacks studied, the clinical seizures were extremely mild. The symptoms were as follows: the subject experienced respiratory depression and simultaneously opened his/her eyes, or in some cases, opened his/her eyes and rotated or bent his/her neck forward very slightly. The authors referred to these attacks as "eye opening seizures." Figure 2B shows the EEG during an "eye opening seizure." The average frequency of spikes at the time at which the attacks began in the third group was 14 ± 0.4 Hz. The spike rhythm displays a high voltage of 100–200 μV. The seizure ended with the mixing in of spike-and-wave and slow waves.

Group in which clinical attacks occur simultaneously with spike discharge

This was seen in 13 of the 42 attacks recorded. Typical seizure symptoms included the patient ceasing to breathe at the same time that the spike discharge began, opening his/her eyes and raising both arms, after which tonicity gradually strengthened to a peak, and muscular tonicity disappearing as the spike discharge completed. In this first group of attacks, all subjects were noted to raise both arms. The EEG showed an average frequency at the start of seizure in 13 attacks of 22 ± 0.6 Hz, with the fast spike discharge beginning at this low amplitude, then gradually increasing amplitude and reducing frequency. In simultaneously recorded nuchal and upper limb muscle electromyograms, muscular discharge began and increased at around the same time as the appearance of 22 Hz spikes on the EEG. An exemplary EEG during the first group of attacks is depicted (Figure 2D). Initially, spike-and-slow complexes occur, followed by flattening in the EEG, then low-voltage 22 Hz spikes. The voltage rises gradually and at the end of the attack, slow waves between 1.5–3 Hz become mixed in, with the pattern eventually changing to slow waves only.

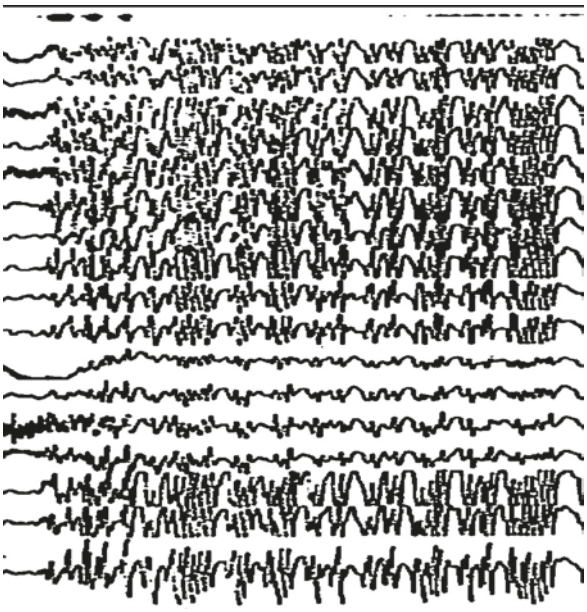
Group in which the clinical attack occurs slightly after the start of spike discharge

The seizure symptom of this group is that the attack comes after the occurrence of a spike discharge, when the spike frequency increases. This was seen 14 out of 42 attacks. The symptoms included the patient opening his/her eyes, having respiratory depression, and either slowly rotating or slowly bending his/her neck forward, and his/her arms becoming tonic and raised, after which the attack progressed in the same way as those in the first group or abortively. An exemplary EEG in an attack in this second group is depicted (Figure 2C). The low amplitude spikes occurring in sleep suddenly become high-amplitude, fast rhythm, then the amplitude becomes a low amplitude fast wave, then once more a high amplitude fast rhythm, which continues until finally it becomes multiple spike-and-wave complexes, before changing to a waking brainwave pattern.

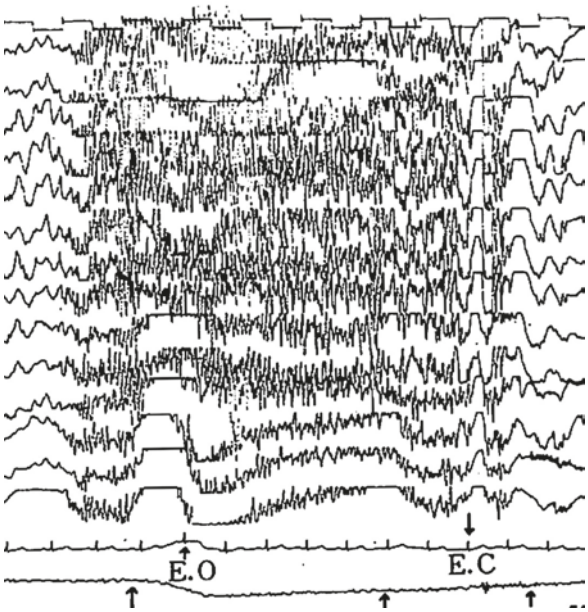
To summarize the frequency changes during the 14 attacks in this second group, the average was 19 ± 0.7 Hz when attacks occurred. When seizures occur, there is no significant difference in spike frequency to that in the first group, with seizure symptoms also similar to those in the first group, although the attacks were less severe. The electromyograms recorded at the same time showed that muscular discharge began in the cervical muscles close to the body axis, with upper limb muscle discharge beginning with the occurrence of a 19 Hz spike discharge on the EEG.

Summary of tonic seizures

Tonic seizures can be categorized by seizure symptoms into generalized tonic seizures, which involve anything from the body axis muscles to all limbs, axial limb tonic seizures, in which the involvement of the limbs is weaker, and axial tonic seizures. It is believed that the first group is global tonic seizures, the second group tonic axorhizomelic seizures and the third group

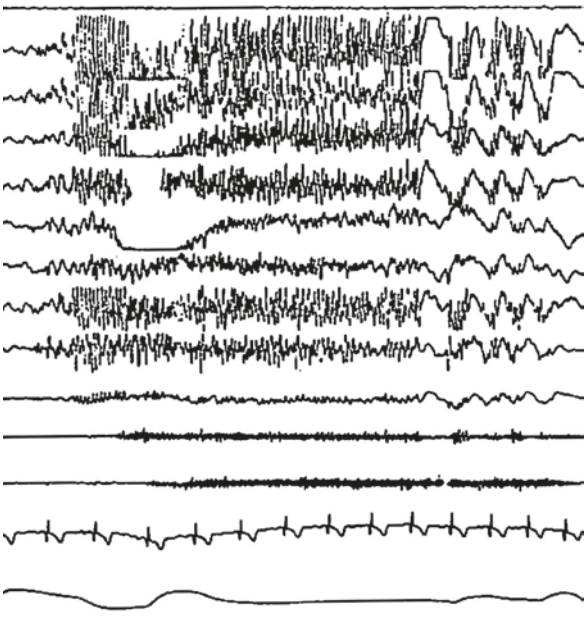


A. Atypical absence

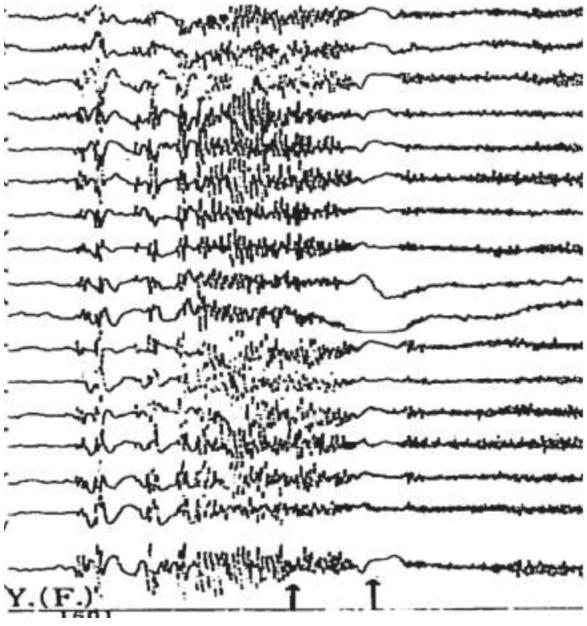


B. Tonic axial (eye opening)

E.O – eyes open; E.C – eyes closed. The first upward arrow indicates eyes closed, the second indicates eyes open and the third indicates eyes closed.



C. Tonic axorhyzomelic



D. Global tonic

The first upward arrow indicates eyes open and the second indicates the beginning of a global tonic seizure.

Figure 2. EEG features during various types of seizures (Yagi et al., 1978; Yagi et al., 1982).

tonic axial seizures. EEGs recorded during the attacks reveal that the first group presents fast waves at a low voltage (around 22 Hz) from desynchronization, the second group displays a range of EEG images from the start of the attack onwards but when seizure symptoms become clear, they become fast waves averaging 19 Hz from mid-range voltage and display the same changes as those in the first group, while the third group present a high-voltage (min. 100 μV), fast rhythm averaging 14 Hz. When tonic seizures occur, the EEGs show a division the group presenting desynchronization, with continual low-voltage fast spikes (approx. 22 Hz), and those with a high-voltage, slower spike rhythm (approx. 14 Hz), as well as some cases in which both states are combined together. These findings are believed to be consistent with those of Gastaut et al. (1963), who reported rapid desynchronization with or without subsequent rapid synchronization and pure hypersynchronization at 10 Hz (epileptic recruiting rhythm). Furthermore, Ohtahara et al. (1970) conducted a detailed analysis based on categorization according to desynchronization, rapid synchronization, recruiting rhythm and "rapid rhythm" (sleep). In addition, Gastaut and Tassinari (1975) conducted a detailed analysis of 1) desynchronization (simple flattening or activation), 2) very fast activity at 20 ± 5 Hz, initial low voltage and progressively increasing amplitude to 50–100 μV, 3) recruiting rhythm (epileptic recruiting rhythm), and 4) slow wave discharges in the theta and delta frequency, very rare.

When considering the occurrence mechanisms of tonic seizures, the authors focused on desynchronization or low voltage fast wave activity, along with generalized tonic seizures/axial limb tonic seizures, as well as high-voltage fast rhythm and the phenomenon of open eyes, respiratory depression and mild cervical muscle tonicity (Yagi and Seino, 1983).

Research into drop attacks

Ikeno et al. (1985) reported on 48 epileptic drop attacks in 17 children using video-EEG monitoring, it which the subject fell to the floor without being able to stand or sit for one second. In all cases, the diagnosis was LGS. According to this report, the clinical symptoms accompanying the falls in the 48 attacks were categorized into the following four groups: a) Tonic type, 9 attacks in five patients; b) Flexor spasms type, 25 attacks in eight patients; c) Myoclonic-atonic type, 12 attacks in three patients; and d) Atonic type, 2 attacks in one patient.

The EEG features at the time of the attacks corresponding to these four types are diverse. Tonic type attacks (9) featured a spike-wave complex (4), polyspike-wave complex (2), fast wave activity (1) or undetermined (2); Flexor spasms type attacks (25) featured a lack of paroxysms (13), high-amplitude slow wave (8) or undetermined (4); Myoclonic-atonic type attacks (12) featured a spike-wave complex (6), polyspike-wave complex (4), polyspikes (1) and sharp wave (1); and Atonic type attacks (2) featured polyspikes (1) and lack of paroxysm (1).

Seizures in which the patient falls over within one second can be categorized into these four types based on detailed studies, with the corresponding EEG at the time of the attacks also being diverse. Of the eight cases categorized as Flexor spasms type, however, seven had transitioned to LGS from West syndrome. The EEG features show a spike-wave complex, polyspike-wave complex, and fast wave activity; furthermore, scalp EEGs show a lack of abnormal seizure waves.

If pressed, it is possible to divide the seizure symptom of falling over into cases with progression of tonicity in the posture-retaining muscles and, on the other hand, cases which loose tension in the posture-retaining muscles.

Research into all-night sleep EEGs in LGS

The all-night sleep of 22 patients with LGS was simultaneously recorded on a polygraph and video-EEG, after which the relationship between attacks and stages of sleep were investigated. The 22 LGS patients were aged between seven and 29 during the study. Sleep stages were determined according to Dement and Kleitman's criteria. However mild the change in behavior, it was assumed to be a seizure phenomenon if it was compatible with the simultaneously recorded epileptic discharge. In 22 patients, a total of 1191 clinical seizures were recorded during all-night sleep. Table 3 shows a summary of the data.

A range of clinical attacks consistent with epileptic discharge can be seen during sleep in LGS patients. Slow spike-wave bursts, polyspike-wave bursts and irregular high voltage slow wave bursts result in myoclonic jerk, eye blinking and respiratory changes, each of which are symptoms that can be accompanied by eye opening. Blinking, respiratory changes and opening the eyes were particularly noticeable as phenomena occurring during an attack. Furthermore, in more than half the cases of attacks occurring during continuous high amplitude spikes, the phenomenon of open-

Table 3. EEG features corresponding seizure manifestations during sleep,total 1191 seizures

1. Ictal EEG: slow spike-wave burst, polyspike-wave burst, irregular high voltage slow wave burst	
Clinical manifestations	**Number of seizuress**
Myoclonic jerk	199
Eye blinking	109
Respiratory changes	107
Eye opening accompanying with blinking, respiratory changes, jerking of face	68
Protrusion of tongue	22
Grimacing	5
Eye movement	3
Bradycardia	1
Total	**519**

2. Ictal EEG: high amplitude spike train	
Clinical manifestations	**Number of seizures**
Eye opening with mild tonic expressions	293
Subtle and gradual tonic movement of neck and arms	70
Jerking of face and /or arms	52
Eye opening with blinking	40
Respiratory changes	39
Eye blinking	25
Grimacing	11
Cardio inhibition	2
Swallowing	2
Total	**534**

3. Ictal EEG: low amplitude spike train	
Clinical manifestations	**Number of seizures**
Subtle and gradual tonic movement of neck	37
Respiratory changes	32
Global tonic seizure	27
Movement of mouth	11
Jerking of face	11
Jerking of head	6
Eye opening with mild tonic expressions	5
Movement of jaw	4
Jerking of arms	3
Opening of mouth	2
Total	**138**

ing eyes accompanying mild tonic symptoms was noted. Continuous low amplitude spikes were accompanied by generalized tonic seizures, milder axial or axial limb tonic seizures and even respiratory changes in extremely mild cases. Attack phenomena include respiratory changes, blinking, open eyes, body axial muscle tonicity and axial limb tonicity or tonicity involving all limbs. This is an important observation when considering how LGS attacks originate. In other words, in contrast with the phenomenon on an EEG, diverse but at the same time qualitative similar muscle tonicity should be used to indicate seizure symptoms, even though it occurs at differing strengths. This indicates that there is a difference between the mechanism for the occurrence of brainwave phenomena and the mechanism for the appearance of seizure symptoms.

Sleep

Of the 22 cases of all-night sleep recorded, in three cases, high voltage slow waves and generalized spikes continued throughout the recording of sleep stages, such that humps and spindles were not clear on the EEG, and the patients were assumed to be in rapid eye movement REM stage, only. Sleep analysis was undertaken in the other 19 cases. A comparison was undertaken with the all-night sleep EEG of one case of childhood absence epilepsy and six cases of benign childhood epilepsy with centro-temporal spikes. The results indicated that 73% of all sleep time in the 19 cases of LGS was stage 1 and stage 2, extremely high compared to the 52% in the comparison group. It appears that attacks, which occur frequently in the first stage of sleep, are prevented by the progression of sleep stages. During the first hour of sleep, subjects were analyzed for sleep stage, wherein, compared to the fact that 14 of 19 cases (73%) remained between stage 1 and stage 2, seven comparison cases had moved swiftly to stage 4 (Table 4). When the frequency of seizures (the number of times they occur in 10 minutes) at each sleep stage was calculated for all 19 LGS cases, it was found that the frequency increases with progression through sleep stages but falls significantly once the subject reaches REM sleep (Figure 3).

In LGS patients, seizure activity is high during slow wave sleep, in turn preventing the progression of sleep stages. This may modulate the brain mechanisms related to sleep and waking, facilitating the occurrence of attacks. Among the all-night sleep polygraph records taken for LGS patients, while REM was confirmed in three cases, the fact that spindles could not be confirmed in the EEG may indicate damage to the spindle formation mechanism.

Generalizations related to LGS, along with observations regarding the epileptogenic mechanism

While LGS usually starts in infancy, in a few cases it can have late onset, at age eight or older (L-LGS). This L-LGS is often seen in patients with a history of encephalitis or encephalopathy, or status epilepticus, suggesting that these factors are the reason for the onset of LGS. At the same time, long-term observation of the prognosis of LGS indicates that the attacks remaining the longest are tonic seizures, suggesting that these are the basis of LGS (Figure 4). Long-term observation indicates that around 30% or more LGS patients retain almost all the basic symptoms of the condition after ten years or longer, while the rest gradually lose the characteristics of the condition, with it becoming residual or progressive in around 60% of cases and effectively relieved in just under 10%.

The authors looked at the characteristics of LGS attacks including atypical absence seizures, drop attacks and tonic seizures. EEG features corresponding to atypical absences are diverse, lasting a short or long period, they are accompanied by atonic symptoms, and the end of the attack tends to be unclear. Drop attacks were categorized into tonic, myoclonic atonic, flexor spasms and atonic type, but can in fact be categorized into those in which the patient falls over due to hypertonia of the posture-retaining muscles and those in which the patient falls over due to loss of tension in the posture-retaining muscles. The former are related to the occurrence mechanism for tonic seizures, while the latter are thought to be related to the sudden inhibition of the mechanism maintaining muscle tension. Tonic seizures range from those manifesting in extreme-

Table 4. Progression of sleep stages within one hour of falling asleep: Comparison of the Lennox-Gastaut syndrome (LGS) group with other epilepsies (childhood benign epilepsy group) without seizures during sleep

	LGS N = 19	Other epilepsies N = 7*
Stage 1 to 4	1	7
Stage 1 to 3	4	0
Stage 1 to 2	14	0

*Other epilepsies: Childhood absence epilepsy-1, epilepsy with CMT foci – 6.
14/19 (73.4%) of LGS with hypnic seizures remained at Stage 1–2, whereas 7/7 (100%) of Other epilepsies without hypnic seizures progressed rapidly to Stage 4.

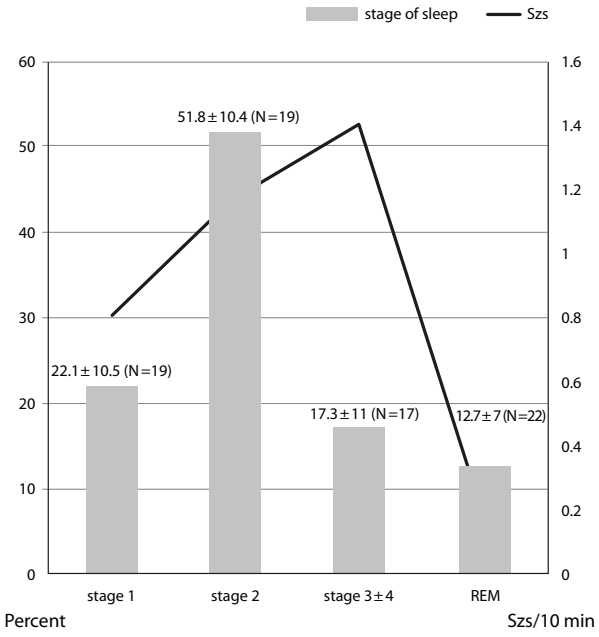


Figure 3. Sleep stage and seizure frequency per 10 minutes

Total sleep: Av.516.3 ± 56 min./night (N = 22 patients)

Total seizures (Szs): 1191

The left side scale represents the percentage for sleep stage and the right side scale represents seizure frequency per 10 minutes.

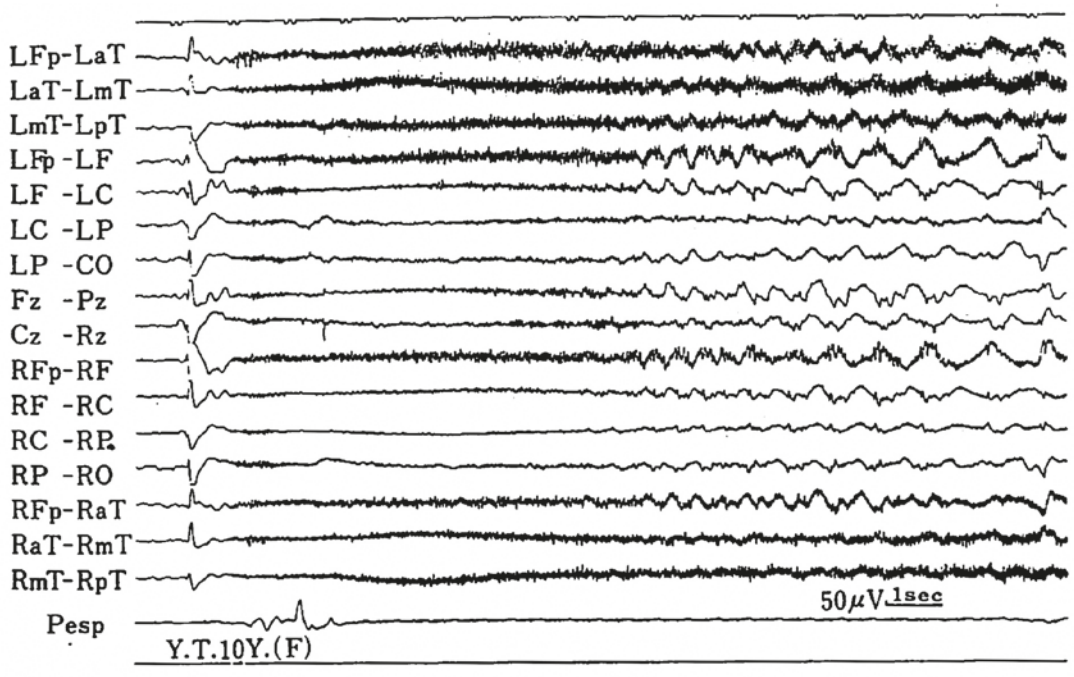


Figure 4. Global tonic seizure (the same patient as shown in Figure 2D, Yagi et al., 1978).

The limbs are tonically extended, the neck is bent slightly forward, is tonic and raised from the pillow. Both eyes are wide open. High-voltage slow waves appearing on EEG indicate tonicity but no clonic seizures are noted. Pesp = respiration. Calibration of EEG record: horizontal bar = 1 s, vertical bar = 50 μV.

ly mild axial muscle tonicity, open eyes and respiratory changes, accompanied by high-voltage fast rhythm on the EEG, to tonic seizures accompanied by tonicity from the axial limbs to peripheral muscles and EEG features present from desynchronization through to low voltage fast activity.

All-night sleep polygraph and seizure symptoms analysis indicate:

1. a relationship between slow spike-and-wave clusters, multiple spike-and-wave clusters, irregular high voltage slow wave clusters and nictation, open eyes, respiratory changes and mild axial muscle tonicity, as well as between high-voltage spike rhythm and open eyes, respiratory changes and axial or axial limb tonicity, and furthermore;
2. between low voltage fast wave clusters and generalized tonic seizures or axial limb tonic seizures.

The following is a consideration of the LGS occurrence mechanism based on the abovementioned clinical symptoms and EEG phenomena.

Epileptogenic mechanisms of tonic axial and tonic axial limb seizures

Firstly, let us consider the tonic axial seizures and tonic axial limb seizures that accompany open eyes during sleep. Open eyes occur because the upper eyelid muscle is raised. The oculomotor nerve controls the muscles that raise the eyelid and is located in the midbrain at the superior colliculus level. Research into sleep and seizures during sleep in LGS has shown that there is a strong connection in the brain structure between seizures and the sleep/wake mechanism. The reticular brain activating mechanism, which is the vital mechanism that maintains brain function, is found in the midbrain reticular formation (Moruzzi and Magoun, 1949). The relationship between the open eyes phenomenon and waking from sleep is physiologically profound. The phenomenon of opening the eyes, from a regular physiological perspective, is seen in relation to epileptic ictal discharge during sleep. It was also noted that immediately after ictal discharge, subjects' sleep became shallower. These two phenomena can be correctly considered, clinically, to indicate that the area of the brain related to the onset of attack is in the midbrain reticular formation. Muscular tonicity during tonic seizures occurs in body axis muscles such as the frontal and temporal muscles, spreading to the limbs and limb peripheral muscles (Miyakosi et al., 1977). The main agent of an LGS attack is tonic seizure and not tonic clonic seizures. Rather, they are characterized by the lack of accompanying clonic components (Figure 5). During a global tonic seizure, the position of tonicity is seen in a strong tonic state, close to decerebrate rigidity. This was considered to be a result of excessive discharge in the brain stem reticular formation. Burnham (1987) summarized the historical perspective on convulsion caused by brain stem stimulation in animals. This supports the opinion of Kreindler et al., (1958), quoted by Gastaut et al. (1963). In regard to the occurrence of tonic seizures, Gastaut et al. (1963) appear to have been inspired not only by the experiments of Kreindler et al. (1958), but also by the detailed reports made by Jackson and Singer (1902) and Jackson and Barnes (1902) on the same case (based on the similarity of clinical symptoms), reasoning that the attack probably originated in the lowest level fit, trunk fit, ponto-bulbal. In the experiments of Kreindler et al (1958), stimulation of the bulbo-ponto-mesencephalic reticular substance and periaqueductal grey matter resulted in emprosthonoid contraction, hyperextension of the limbs and powerful flexion of the head and trismus, with fine clonic spasms of extremities being finally superimposed. Desynchronization was manifested in 90% of cases. This attack was induced even in cats undergoing precolliculus section. More recently, Velasco and Velasco (1990) emphasized the mesencephalic reticular formation (MRF) was necessary for the occurrence of tonic generalized seizure. At the same time, they indicate the EEG seizures (believed to indicate the ictal discharges expressed on the electroencephalograph) are completely unrelated to MRF. This is the same as the second theory expounded at the end of the paper by Kreindler et al. (1958), in other words, "the functional characteristics of reticular circuits have peculiarities which make them differ very much from cortical ones". In LGS, generalized tonic seizures occur and EEGs show the occurrence of the desynchronization (Figure 4) indicated in experiments by Kreindler et al. (1958). As such, if MRF is contributing to the occurrence of attacks in LGS, this makes the tonic seizure symptoms analyzed to date easier to understand. Recently, detailed research has been conducted into medullary reticular formation (MeRF), with Petersen et al. (1978) and Petersen et al. (1979) indicating that MeRF contains somatotopographycal organization. It has also has been stated that in experiments, the output from the

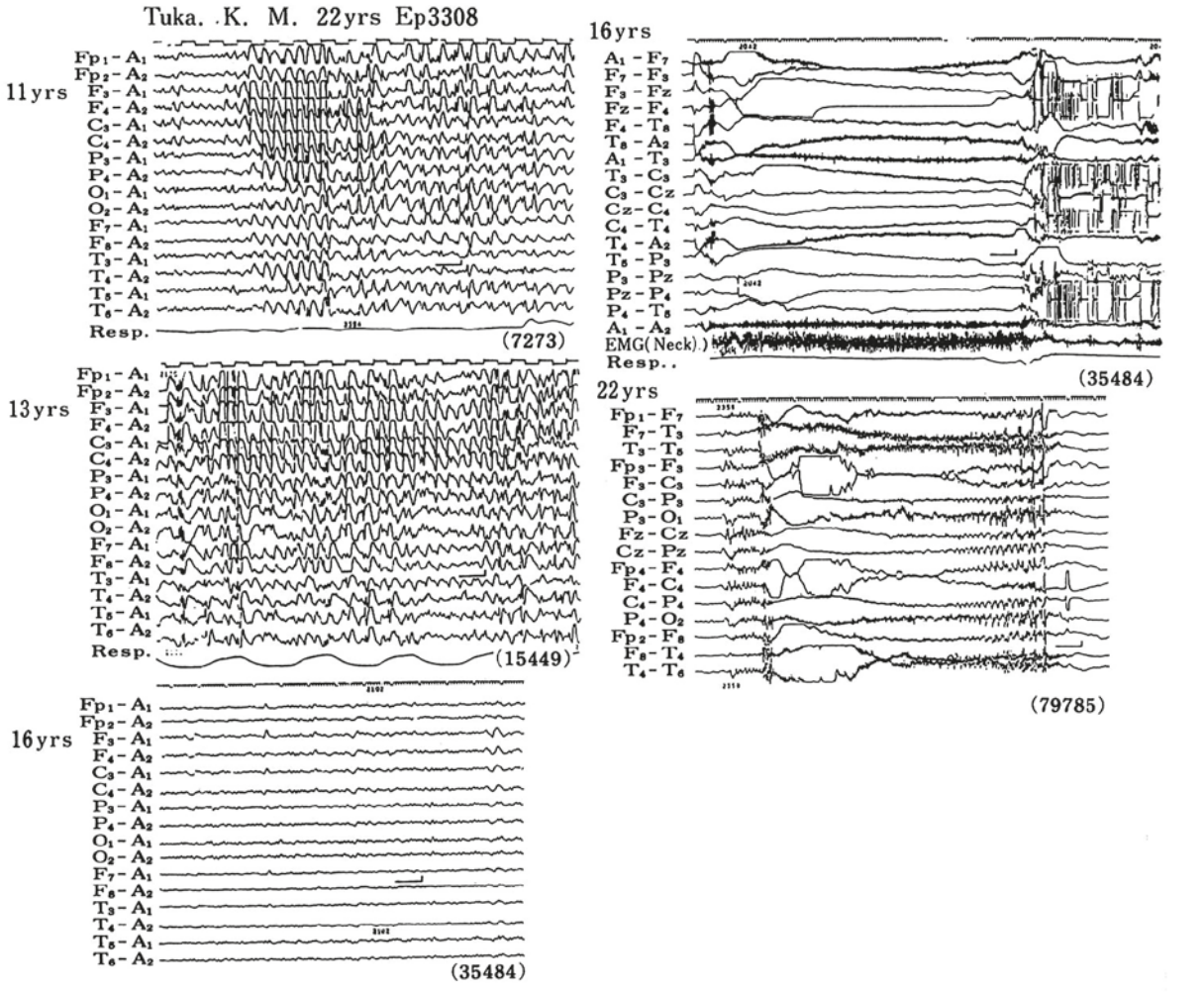


Figure 5. Long-term follow-up EEG in a patient with Lennox-Gastaut syndrome.

Left upper EEG – age 11 years; left middle – age 13 years; left lower and right upper EEG – age 16 years; right lower EEG – age 22 years.

Disappearance of atypical absence but continuance of nocturnal tonic seizures at the age of 22 (Yagi K., 1990). Calibration of EEG record – horizontal bar = 1s, vertical bar =50 μV.

pedunculopontine tegmental nucleus (PPN) between the midbrain and the outer tegmentum of pons to the reticular formation is related to the whole-body state of tension via the reticulospinal tract (Takakusaki et al., 2001; Habaguchi et al., 2002; Takakusaki et al., 2003). Furthermore, it has been shown in cats that the most reticulospinal neurons project bilaterally to entire spinal segments from the cervical to the sacral cord and control motor neurons innervating neck, head, trunk and leg muscles (Takakusaki and Okumura, 2008). This corresponds in human tonic seizures to the state in which tonicity gradually progresses from the nuchal muscles and axial muscles to the axial limbs and finally to the distal muscles, and indicates that humans also have a similar functional structure. Furthermore, projection from the PPN to the thalamus non-specific nuclei configures part of the ascending reticular formation activating system and may be related to sleep/waking.

Epileptogenic mechanisms of atonic seizures

While atonic attacks were believed to result from the sudden loss of tension in posture-retaining muscles, details of the mechanism behind their occurrence are unclear. Recently, research on cats by Takakusaki et al. (2001) and Habaguchi et al. (2002) revealed that providing a 30 μA stimulus to the area equivalent to the MeRF medial part and nucleus reticularis giganantocelularis results in decerebrate cats losing muscle tone,

while the stimulating the dorsal part nucleus reticularis magnocellularis in the same area results in muscle tone increasing tonically and/or phasically. Taking these results into consideration, it is believed that epileptic discharge fired at MeRF could result in sudden muscle tension loss or in sudden increasing muscle tonicity, or alternatively, cause the failure of posture-retaining function due to muscle hypotonia or muscle hypertonia.

Epileptogenic mechanisms of atypical absence

Despite this, however, the basis for the occurrence of atypical absence seizures cannot be understood merely from MRF and the possibility that the thalamo-cortical system also contributes in some way (Avoli, 2012) cannot be ignored. Velasco et al. (1991) succeeded in recording slow spike-wave complexes, fast rhythm in LGS centromedian thalamic nuclei. The EEG recorded by the authors during atypical absence seizures had poor rhythm but a 20 Hz fast rhythm bilaterally occurring slow spike-and-wave complexes (1.5–2Hz) along with a 12 Hz fast rhythm, or included spindle-like waves (Figure 1). The start and end of absence seizure symptoms were roughly related to the start and end of seizure discharge on the scalp EEG, appearing as though someone literally flicked an on-off switch. For this reason, we considered the relationship between reticular formation and the thalamus. Anatomically, reticular ends in the upwards direction, thereby enclosing the thalamus rostral, lateral and ventral surfaces (Ranson and Clark, 1959). In animal experiments, this thalamic reticular neuron was entirely GABAergic and was a sleep spindle pacemaker (Steriade et al., 1987). At the same time, in feline generalized penicillin epilepsy, where lesions were created in the MRF and penicillin administered by intramuscular injection, it was demonstrated that spindles changed into a spike-wave pattern (Kostopoulos et al., 1981). As a result, it has been demonstrated that the thalamo-cortical system contributes to spike-wave discharges. Gloor et al. (1990) believe that in order for spindle to change into spike-wave discharges, "penicillin induced increased excitability of cortical neurons which is responsible for the secondary recruitment of a powerful, presumably recurrence, intracortical inhibitory mechanism" is required. In clinically considered LGS, MRF has epileptogenecity and if we believe that it is causing abnormal activity in the ascending cerebrum activation system, then it can be assumed that acceleration of cortical neuron excitability, similar to that induced by penicillin, exists. Steriade and Contreras (1998) suggest that " inhibition of thalamo-cortical cells and their incapacity of relaying coming signals in their root to cortex may explain the impairment of consciousness during SW seizure".

Generalization concerning the epileptogenic mechanisms of LGS

Timofeev and Steriade (1998) propose as to the thalamocortical augmentation (Morison and Dempsy, 1942, 1943) that hyperpolarization-dependent low-threshold augmenting responses in the thalamo-cortical neuron are mainly due to incremental responses in the GABAergic thalamic reticular neuron, and that depolarization-dependent augmenting responses are caused by decremental responses in the thalamic neuron, related to excitable impulses. The thalamo-cortical network is important in their research (Timofeev et al.,1998), and it is believed that the expression of ictal discharge seen on the EEG via the network (spike-wave complexes and fast components) is implemented in the cortex (Steriade et al., 1998; Neckelmann et al.,1998; Timofeev and Steriade., 2004). In order to prove their theory, the authors stimulated mesopontine cholinergic nuclei and used an activating depolarizing system, consequently, more consideration needs to be given to the importance of the contribution of the thalamic reticular neuron to the thalamo-cortical network. In other words, the contribution of the reticulo-thalamic system on the thalamo-cortical system is important (Min, 2010) in that, it is believed that brain stem reticular formation epileptic discharge causes functional abnormalities to occur within the thalamic reticular neurons, causing atypical absence seizures as a result. Halasz (1996) activated generalized repetitive fast discharges (GRFD) in human LGS subjects by administering diazepam and observed the phenomenon whereby it was deactivated using flumazenil. Furthermore, the administration of diazepam is known to induce attacks, making them worse (Tassinari et al., 1972; Prior et al., 1972; Ohtsuka et al., 1982). Based on the theory of Steriade (1998), diazepam is a GABAmimetic drug which may act on the thalamic reticular neurons, causing hyperactivation and leading to hyperpolarization in the thalamocortical neurons. As a result, GRFD may occur as a hyperpolarization sensitive low threshold augmentation response. The benzodiazepine antagonist flumazenil deactivates this condition. GRFD is what we refer to as high voltage fast spike. As we have already emphasized, Halasz (1996) believes, given the close re-

lationship between spike-wave discharges and GRFD, that GRFD is a derivative of spike-wave patterns. The clinical findings of this researcher may prove the theories of Steriade. If the EEG of a patient during an attack is observed, as shown in Figure 2, the EEG during 2A atypical absence seizures are 20 Hz high-voltage fast rhythm waves combined with a polyspike-wave complex, while during a 2B open eyes attack, they were a 14 Hz high-voltage fast rhythm, during 2C axial limb tonic seizures, they change from high-voltage fast rhythm to even faster wave activity, and in 2D sleeping generalized tonic seizures, they are seen to undergo desynchronization from 14 Hz high-voltage fast rhythm to low voltage fast waves. From the perspective of EEG features, high-voltage fast wave rhythm has the same expression pattern, indicating an augmenting response originating in the thalamus and, similarly, multiple spike-and-wave complexes and spike- and- wave complexes can be seen, which are expressed on the EEG due to activity in the thalamo-cortical system. Desynchronization or low amplitude wave fastening, however, indicate a state of lower brainstem activity in the EEG and appear to come via the ascending reticular activating system (Moruzzi and Magoun, 1949) or may be partly as depolarization-dependent augmenting responses being caused by decremental responses in the thalamic reticular neurons. The clinical symptoms of LGS, including the major attacks (tonic seizures, atypical absence seizures and atonic seizures), cannot be understood unless they are thought to originate in the reticular formation and become understandable if we consider that the expression of the EEG is being expressed via the thalamo-cortical system. This provides a response to the indication by Seino et al. (1980) that there is a paradox in the relationship between generalized seizure symptoms and EEG expressions. Bremer (1961) had already indicated a dissociation between behavior and electrocortical appearance following atropine administration. In other words, EEG expression and behavior expression were not the same thing.

In a series of studies by Steriade et al. (1998) using LGS model animals, the authors attempted to clarify the connection between the thalamic reticular neurons and the thalamo-cortial system. Within the pathological condition known as epilepsy, LGS could be said to be the human model that clearly demonstrates the difference in function between the reticular system and the cortico-thalamic system.

Based on consideration of these EEG features and clinical symptoms, LGS epileptic native lesions become easier to understand if it is considered that they exist between the mesencephalic reticular formation and the thalamic reticular system. The fact that this reticular system becomes epileptogenic is the reason for its incurability. This is due to the fact that all centripetal input distributes information here, while a wide range of centrifugal output is also thought to distribute information here, with result that the reticular system acquires epileptogenecity, and once stimulated, becomes naturally difficult to treat. Observations of this type of activation have been indicated by Siniatchikin et al. (2011) using EEG-fMRI. This is considered to be one form of proof. It is hoped that LGS will come to be considered as an epileptic reticulo-thalamo-cortical system disorder.

CONCLUSION

Based on clinical and neurophysiological research, LGS was found to be a reticular system disorder, in which the reticular system between the midbrain and the thalamus becomes epileptogenic and is activated, or in other words, caused by self-sustained epileptogenecity. LGS is believed to be an epileptic reticulo-thalamo-cortical system disorder. Furthermore, reticular formation is believed to be the main neural substrate contributing to symptomatic generalized epilepsy.

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CONFLICT OF INTEREST DISCLOSURE

The author has no conflict of interest to declare.

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