On Lennox-Gastaut Syndrome

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INTRODUCTION

Lennox-Gastaut syndrome is present in approximately 4.0% of epileptic children. It is not amenable to treatment and accounts for a large proportion of so-called refractory epilepsy cases[1]. Specific causes of this syndrome have not been firmly established yet and, allegedly, there are a variety of underlying diseases or presumed etiologic factors. Thus, at the present time, one can only say that the syndrome is polyetiological in nature. The purpose of this paper is to present the results of a computerized tomographical (CT scan) study, clinical trial with anticonvulsants and a follow-up observation of EEG for a maximum of 3 years.

SUBJECTS

This series consisted of 6 males and 3 females with an age range of 10 to 24 years. The age at onset ranged from 11 months to 10 years 3 months. Although none had a family history of convulsive seizures, the mother and an elder sister of one patient (Case 7) had mental subnormality. Chromosomal abnormalities were not observed in any case.

PAST HISTORY

Past history revealed febrile illnesses (40°C or over) in 5 cases, neonatal asphyxia in 1 case, toxemia of pregnancy in 1 case, dystocia in 1 case and nothing significant in 1 case.

CLINICAL SYMPTOMS

Clinical symptoms were predominated by tonic spasms, tonic seizures and atypical absence, and included myoclonic absence, atonic seizures and clonic seizures. Mentality had seriously deteriorated in 6 cases, was

moderately retarded in 2 cases and slightly abnormal in 1 case.

CT SCAN FINDINGS

Seven of the 9 cases provided abnormal CT scan findings, which varied from case to case in type, location and degree. Cases 1 and 2 provided no morbid or abnormal findings upon CT scan.

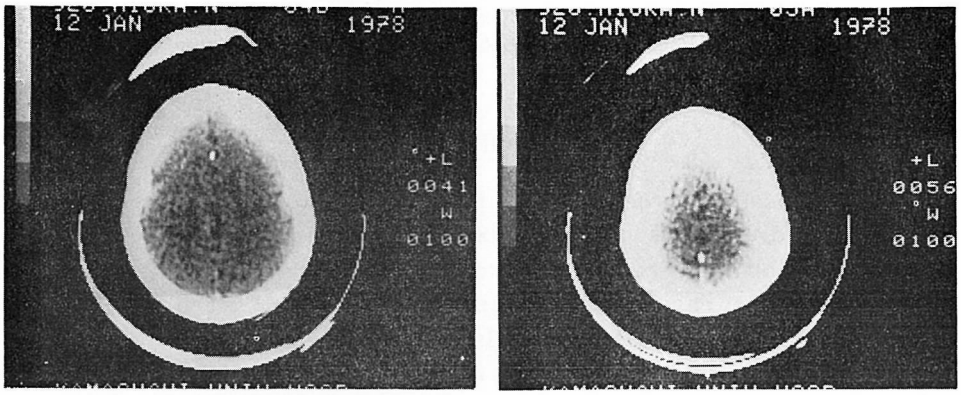

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Fig. 1 a) A high density mass in the anterior portion of the falx cerebri. 4B. (Case 3).
b) Calcification of the posterior portion of the falx cerebri. 5A.

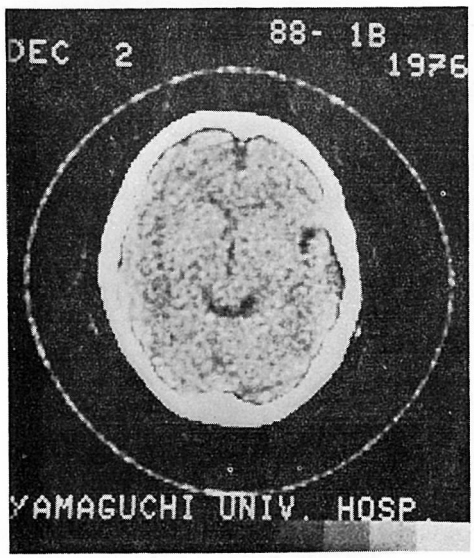

Fig. 2 Atrophy at its pole of the right temporal lobe, a widening of the right lateral fissure. 1B. (Case 4).

Fig. 1 a) and b) represent CT scans of Case 3. Evidence of calcification was noted in the anterior and posterior portions of the falx cerebri. Plain skull x-ray permitted inference that these changes represent an organized obstruction of vessels.

Fig. 2 shows CT scan findings obtained from Case 4, which has been reported already[2]. The lateral cerebral fissure was enlarged near the right temporal pole, and the right temporal lobe, as a whole, tended to be slightly atrophic.

Fig. 3 a), b) and c) illustrate CT scans of Case 5. Marked atrophy of the cerebral substance, localized to the right temporal lobe at the

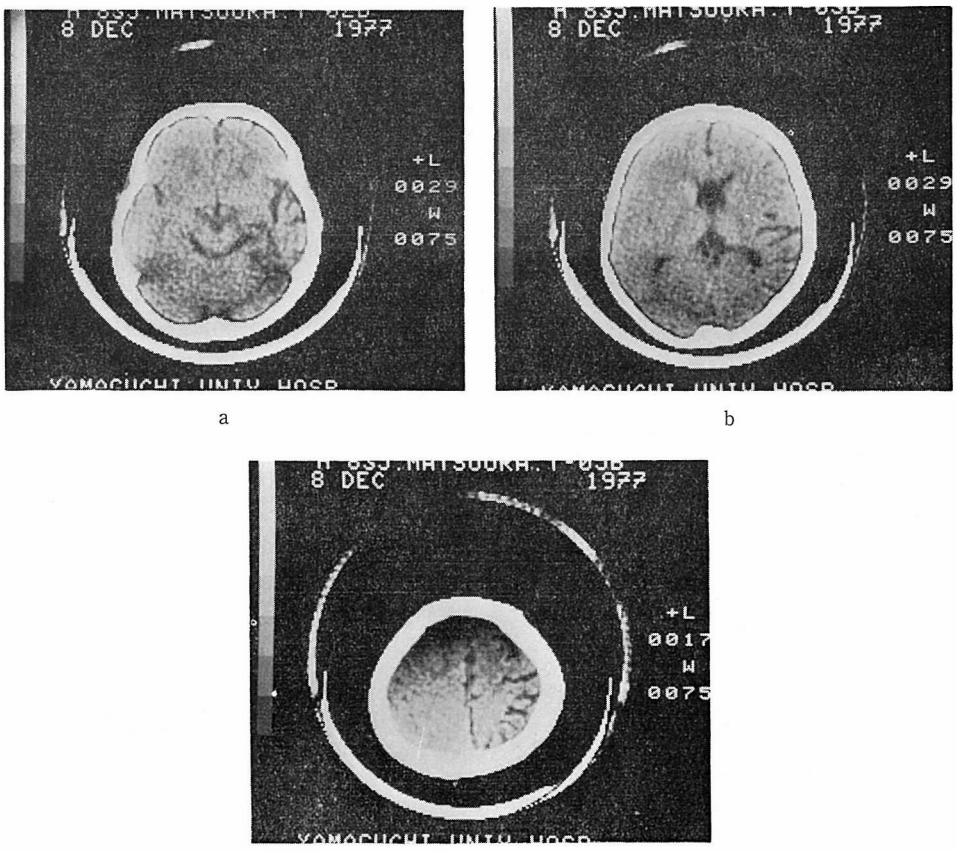

Fig. 3 a) A wide opening of the right fissura latealis is prominent. The right temporal lobe shows evidence of ulegyria. A low density area is seen in the subcortical white matter in the right occipital region. 2B. (Case 5).
b) Cavum septi pellucidi and ulegyria of the right temporal lobe. 3B.
c) The fornix of the right hemisphere showing cerebral atrophy. 5B

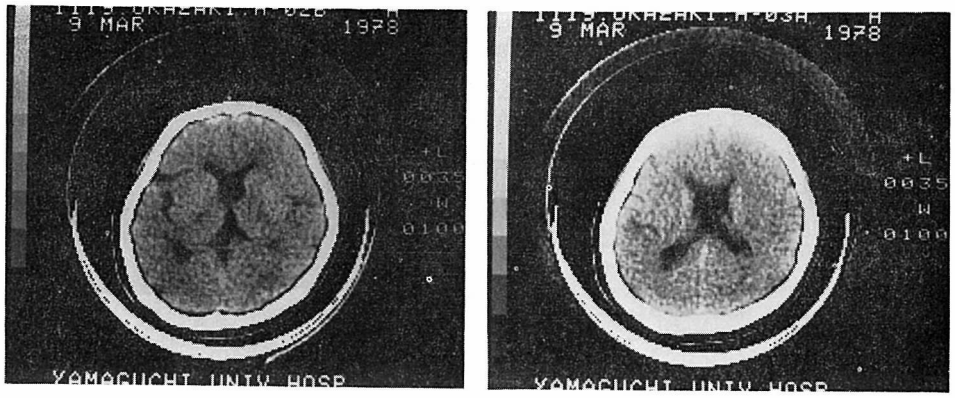

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Fig. 4 a) The cerebral ventricles are enlarged, the left lateral fissure is widened and the left temporal lobe atrophies. Similar changes, though of a slight degree, are present in the right temporal region. 2B. (Case 6).
b) Enlargement of the ventricles and atrophy of the left temporal lobe. 3A.

basal level and involving the whole right hemisphere at the convex, was seen. The brain image in this latter cortical area was that of ulegyria. The right ventricle seemed to be enlarged and a cavum septi pellucidi was demonstrated.

Fig. 4 a) and b) are CT scans of Case 6. The left temporal lobe showed an extensive area of atrophy. Especially marked was the change in that portion of the left temporal lobe adjacent to the lateral cerebral

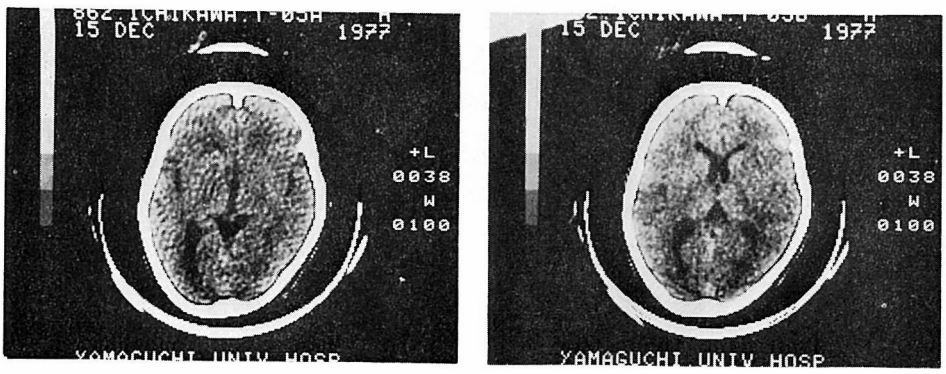

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Fig. 5 a) Atrophy of the temporal lobe bilaterally, enlargement of the posterior horn of the posterior horn of the left lateral ventricle. 3A. (Case 7).
b) Enlagement of the posterior horn of the left lateral ventricle and low density areas seen around the posterior horn of the lateral ventricle bilaterally. 3B.

fissure and, above all, in an area in the proximity of the temporal pole and the posterior limb of the lateral cerebral fissure. The frontal gyrus was found to be atrophic in its anterior horizontal ramus area. In the convex cortical area, the sulci separating the temporal superior and middle gyrus were widely opened. The lateral ventricles were markedly enlarged.

Fig. 5 a) and b) represent CT scans of Case 7. Bilateral atrophy of the temporal lobe was prominent. Furthermore, an extensive low density area was present in the subcortical areas about the lateral ventricle in both occipital regions. Although the nature of this lesion is still unclear, it remains to be ascertained whether or not it represents one of the neuropathological correlations of Lennox-Gastaut syndrome. In addition, a low density area was recognized bilaterally in the region surrounding the thalamus.

Fig. 6 a) and b) show CT scans of Case 8. Prominent findings were an enlargement of the lateral ventricle, a widening of the cerebral sulci in general and an enlargement of the longitudinal fissure of the cerebrum, a finding suggesting atrophy of the whole brain.

Fig. 7 a) and b) show CT scans of Case 9. As can be seen, there was a huge hydrocephalic distension of the lateral ventricle which occupied thebulk of the left cerebral hemisphere. The cortex appeared as a thin-layered structure and there was no evidence of perforated

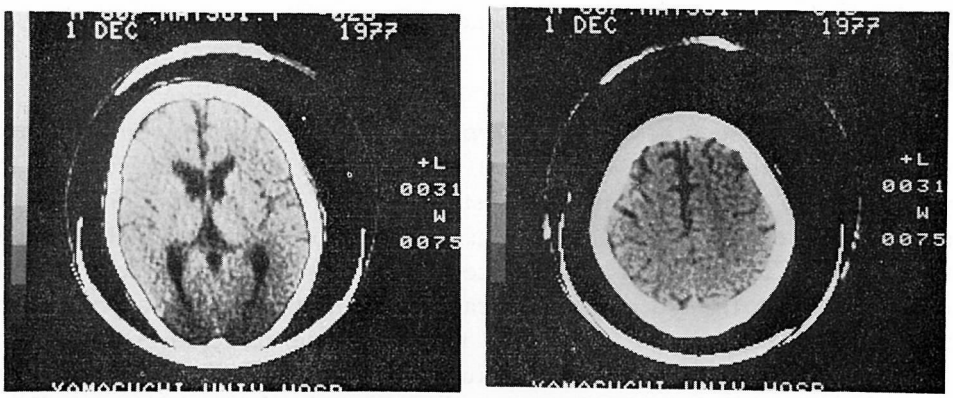

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Fig. 6 a) The ventricular system is generally enlarged, the cerebral sulci tend to be widely opened especially in the frontal and temporal regions. The cerebrum is diffusely atrophic. The subcortical white matter of the occipital lobe shows low density. 2B. (Case 8).

b) The cerebral sulci are markedly enlarged and the longitudinal fissure of the cerebrum is widened in its anterior half. 4B.

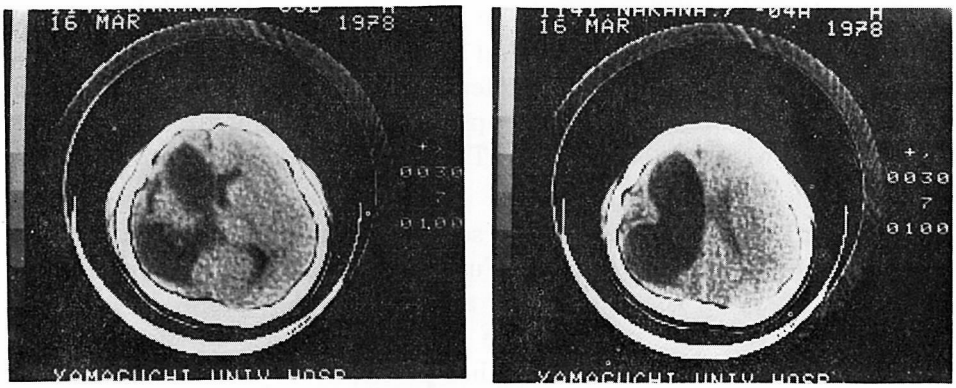

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Fig. 7 a) A superfluous enlargement of the ventricles predominant at the anterior and posterior and posterior horns of the left lateral ventricle. The cortex persists in the temporal and occipital regions. Wide opening of the left fissura lateralyis is prominent. The left side of the skull is hypoplastic. 3C. (Case 9).
b) The left temporal lobe is enlarged as a whole. There is no appreciable shift of the midline. 4A.

brain. Hypoplasia of the above disorder, was noted. The right lateral ventricle was also found to be enlarged, though only slightly.

EEG FINDINGS AND EFFECT OF ANTICONVULSANTS

All of the 9 cases provided EEG findings characteristic of Lennox-Gastaut syndrome, i.e. slow spike-and-wave complex, recruiting rhythm and rapid rhythm.

In this study, ACTH (Cases 1 and 2), sodium valproate (Cases 3 and 8), primidone (Case 4), nitrazepam (Case 5), carbamazepine (Case 6) and clonazepam (Case 7 and 9) were administered respectively to patients with the syndrome to investigate their effects on EEG. Marked suppressant effects on EEG abnormalities was observed in 2 of 2 cases receiving ACTH, in 1 of 2 cases treated with sodium valproate and 1 of 1 primidone treated case. Moderate EEG improvement was noted in 2 cases with clonazepam, in 1 case with carbamazepine, in 1 case with nitrazepam and in 1 case with sodium valproate. All the treated cases began to show EEG improvement within 1 week after starting medication. However, whereas there was an improvement of clinical symptoms in 3 of the 9 cases (i.e., Cases 1 and 2 both receiving ACTH and Case 3 treated with sodium valproate). there was no distinct association between EEG improvement and suppression of attacks in the remaining 6 cases.

Table 1. Clinical Symptoms, Changes in EEG Fidings and CT Findings in Lennox- Gastaut Syndrom Peatients

Case No.	Sex & Age	Age at onset	Past history	Family history	Clinical symptoms	Changes in EEG findings	CT findings	Drugs used	EEG improvement
1	F 10y	5m	toxemia of pregnancy	—	mild mental deficiency (WISC: verbal test 48, performance test 54), atonic seizure, tonic spasm	diffuse polyspike & wave, recruiting rhythm, rapid rhythm→sharp wave localized to left temporal region	no abnormalities	ACTH	++
2	M 17y	11m	pneumonia (at age of 11m)	—	severe mental deficiency (presumed mental age: 2 yrs.) hyperkinetic, tonic, clonic seizures, tonic spasm, atonic spasm, generalized seizures	diffuse very slow spike & wave, recruiting rhythm →generalized short burst of epileptic discharge	no abnormalities	ACTH	++
3	M 24y	2y	high fever from unknown cause (at 6 yrs.)	—	severe mental deficiency (IQ: 20), dromomania, atypical absence, tonic clonic seizures, atonic spasm	diffuse polyspike & wave →diffuse spike & wave	falx calcification	sod. valproate	++
4	M 10y	1y 6m	high fever from unknown cause (1y 6m)	—	severe mental deficiency (IQ: 25), hyperkinetic, tonic clonic seizures, atonic spasm, myoclonic seizures	diffuse polyspike & wave, cluster of the fast activity→ diffuse spike & wave	atrophy of right temporal pole	primidone	++
5	F 16y	10y	neonatal asphyxia, kernicterus	—	moderate mental deficiency (IQ: 42), tonic, atonic spasm, atypical absence, generalized seizure	diffuse polyspike & wave →spike discharge localized to right hemisphere	extensive atrophy of right temporal lobe, ventricular enlargement	nitrazepam	+
6	M 13y	3y	fever of unknown etiology (at 1y)	—	severe mental deficiency, hyperkinetic, tonic clonic seizures, tonic spasm, myoclonic seizures	diffuse polyspike & wave, recruiting rhythm→ single spike localized to left temporal region	enlargement of left lateral ventricle	carbama-zepine	+
7	M 12y	10y 3m	neonatal asphyxia	mother & elder sister, mentally deficient	severe mental deficiency, hyperkinetic,tonic, atonic seizures, tonic spasm	diffuse spike & wave, recruiting rhythm, cluster of the fast activity →diffuse spike & wave	cortical atrophy of temporal lobe	clonazepam	+
8	M 11y	7y	—	—	severe mental deficiency, hyperkinetic, tonic, clonic seizures, tonic spasm	hypsarrhythmia, diffuse spike & wave, rapid rhythm, recruiting rhythm → spike discharge localized to right anterotemporal regin	atrophy of right hemisphere, ulegyria, right ventricular enlargement cavum septipellucidi	sod. valproate	+
9	F 15y	4y	dystocia	—	mild mental deficiency (WISC: verbal test 55, performance test 30), right cerebral palsy, tonic seizure, atonic seizure, atypical absence	diffuse very slow spike & wave→low voltage of left hemisphere	left skull hypoplasia, left hydrocephalic ventricular distension	clonazepam	+

As for improvement in EEG findings, diffuse spike-and-wave complex disappeared in 6 of 9 cases, the recruiting rhythm disappeared in 5 of 5 cases, and rapid rhythm and cluster of fast activity disappeared in 4 of 4 cases. As a result of suppression of these abnormal wave forms, a focalized sharp wave or single spike and low voltage became predominant EEG features in 5 of 9 cases. Most of the foci were located in the temporal area either on the left or right side. After undergoing these changes, EEG findings were not necessarily consistent with cranial CT scan findings but did not aggravate so long as anticonvulsant medication was continued. EEG improvement tended to be more marked in those cases in which no, or trivial if any, CNS abnormalities were demonstrated by the cranial CT scan.

A summary of the above-mentioned information is given in Table 1.

DISCUSSION

Lennox-Gastaut syndrome is polyetiologic in nature and is based on a wide variety of underlying pathologic conditions that are difficult and awkward to classify. This makes the prognosis of this syndrome quite difficult to evaluate. Kruse[3] classified the syndrome into 3 groups, i.e., nuclear group, early onset group and marginal group. The nuclear group is associated with brain damage, begins with a generalized seizure at the age of 2 to 4.5 years, and later develops seizures typical of this pathological entity, whose frequency thereafter is ever-increasing. The early onset group has its onset before 2 years of age. The initiatory symptom is a generalized seizure, which is followed by tonic spasms. To this group belong cases of transition from West syndrome. The marginal group is later in onset than the former 2 groups, the first seizure occurring at more than 5 years of age. The predominant type of seizure is atypical or myoclonic absence. Mental deficiency is mild and the prognosis is relatively good.

According to Otahara[1], the predominant type of seizure of Lennox-Gastaut syndrome patients shifts with age, usually to astatic seizure or generalized seizure and, very rarely, to partial epilepsy.

Diffuse slow spike-and-wave discharges seen with Lennox-Gastaut syndrome, because of their appearance in extensive bursts that are nearly synchronous on both sides, are considered to be of subcortical, notably mesodiencephalic origin. Jasper et al. [4] reported that electrical stimulation at 3 Hz of the central endomedullary plate nucleus of the thalamus was followed by the emergence of diffuse spike-and-wave discharges on the electrocorticogram. Dempsy et al.[5] recognized that

continuous electrical stimulation at 5-15 Hz of the midline nuclei of the thalamus gives rise to a recruiting response. This response bears a close resemblance to the paroxysmal waves seen in Lennox-Gastaut syndrome, and was called burst of rhythmic spike-and-wave by Gastaut et al[6]. It has been hypothesized that rapid rhythm and recruiting rhythm represent epileptic discharges of different frequencies from the endomedullary plate nucleus of the thalamus[1]. Furthermore, both of these rhythms appear only during sleep, a fact suggesting their close relation to the system for the maintenance and regulation of sleep. Kreindler et al[7]. reported that the electrical stimulation of the mesencephalic reticular formation was followed by the development of tonic seizure. They pointed out that this electroconvulsive effect presupposes the use of immature animals, implying the importance of immaturity of the brain.

Hypsarrhythmia of epileptic children may change to diffuse slow spike-and-wave at around 1 year of age. It seems that as the brain matures, a further change to typical spike-and-wave occurs gradually at about 15 years of age. As age advances further, a shifts to abnormal EEG with focus becomes progressively evident. However, even in the presence of a localized CNS disorder, the basic pattern is usually devoid of focalization, this being particularly true with younger children. In our cases, the frequency of appearance of rapid rhythm decreased rapidly from about 15 years of age. All of these EEG changes are presumed to be related to the degree of brain maturity.

Turning to the effects of drugs on EEG in Lennox-Gastaut syndrome, it is said that a drug is proven effective if it produce improvement in both EEG findings and clinical symptoms within 1 week after initiating medication in more than half of the cases and almost all cases begin to improve within 4 weeks of treatment.[8] Such EEG finding as the disappearance of diffuse spike-and-wave, recruiting rhythm, rapid rhythm and cluster of fast activity may be observed. The spike component is also markedly diminished, if not swept away. These drug-induced alterations in EEG pattern may be said to be in good agreement with those associated spontaneous EEG changes which occur with advancing age, i.e., diffuse EEG changes are supereseded by the unilateral temporal lobe focus or, in other words, focalization comes to the fore. This fact, combined with a report of Niedermeyer et al.[9] stating that temporal lobe lesions are accompanied by the appearance of diffuse slow spike-and-wave, which is gradually replaced by focal spikes, deserves much attention from those who are concerned with the clarification of the true pathology of Lennox-Gastaut syndrome.

A close follow-up study of CT scan findings and changes in EEG findings produced by antiepileptic drugs will certainly provide important clues in the elucidation of the pathophysiology of this syndrome as well as to the proper evaluation of its prognosis.

SUMMARY

CT scan findings and changes in EEG findings following the administration of antiepileptic drugs (ACTH, sodium valproate, primidone, nitrazepam, carbamazepine and clonazepam) in 9 cases of Lennox-Gastaut syndrome were reported. CT scan abnormalities, including hydrocephalic ventricle distension, ulegyria, cavum septi pellucidi, temporal lobe atrophy, diffuse cerebral atrophy, ventricular enlargement and falx calcification, were noted in 7 of these 9 cases. Febrile illness, neonatal asphyxia, toxemia of pregnancy and dystocia were considered to be possible etiologic factors. Improvement in EEG findings became evident within 1 week after the start of medication. In all of the 5 cases displaying recruiting rhythm and in all of the 4 cases exhibiting rapid rhythm or cluster of fast activity, these abnormal wave forms were made to disappear. Diffuse spike-and-wave, which was present in all 9 cases initially, disappeared in 6 cases. In the remaining 3 cases, a diminution of the spike component was noted. However, there were instances in which clinical symptomatology did not parallel EEG findings. As medication was continued further, residual EEG abnormalities tended to be focalized in the temporal region. These drug-induced alterations in EEG pattern are considered to provide valuable information for the clarification of the underlying pathology of Lennox-Gastaut syndrome which is known to be age-dependent.

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