Treatment and Long-Term Prognosis of Myoclonic-Astatic Epilepsy of Early Childhood

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Abstract

Purpose: We retrospectively studied patients with myoclonic-astatic epilepsy of early childhood (MAE) to investigate the most effective treatment and long-term seizure and intellectual prognosis.

Subjects: Eighty-one patients with MAE were recruited from among 3600 patients with childhood epilepsy according to the ILAE criteria of MAE.

Methods: We retrospectively investigated the clinical characteristics and ultimate prognosis of the patients with MAE from the medical records. The effects of various antiepileptic drugs, ketogenic diet and ACTH treatments on myoclonic-astatic seizures (MS/AS), apparently a hallmark of this unique epileptic syndrome, were also studied.

Results: MS/AS in 89% of the patients disappeared within 1 to 3 years despite initial resistance, but generalized tonic-clonic or clonic seizures [G(T)CS] tended to continue. The most effective treatment for the MS/AS was ketogenic diet, followed by ACTH and ESM. At the last follow-up, 55 patients or 68% of all the patients had remission of epilepsy, 11 patients or 14% experienced a recurrence of GTCS after a long remission period but easily regained control, and the remaining 15 patients or 18% continued to have seizures and intellectual outcomes were poor. In one half of these patients with poor outcomes, repeated minor epileptic status and nocturnal generalized tonic seizures persisted. A family history of epilepsy and a combination of minor epileptic status are risk factors for poor outcomes.

Conclusion: MAE is considered to form a clinical spectrum ranging in its main seizure type from myoclonic to atonic, and in seizure and intellectual outcomes from benign to malignant. The overall prognosis, despite initial resistance to treatment, appears to be much better than originally thought when ILAE definitions excluding SME are followed.

Key words
Myoclonic-Astatic Epilepsy · Long-Term Prognosis · Treatment Response · Myoclonic-Astatic Seizures · Doose Syndrome

Introduction

Myoclonic-astatic epilepsy of early childhood (MAE) was first described by Doose and has been included as cryptogenic or symptomatic epilepsy with myoclonic-astatic seizures in the International Classification of Epileptic Syndrome [8,34]. It has long been argued about the classification of cryptogenic or idiopathic myoclonic epilepsies during childhood [1,2,4–6,10–12, 18,20,23,35], and the current ILAE has finally recognized four distinct epileptic syndromes including MAE, benign and severe myoclonic epilepsy in infants defined by Dravet [11,12], and cryptogenic (myoclonic variant of) Lennox-Gastaut syndrome (LGS) [34], although the last one is not a true myoclonic epilepsy. Although there have been a number of publications on the clinical and EEG characteristics in the latter three syndromes from many different authors [3,13,22,29,31,33,36], MAE has received attention mainly in relation to nosological issues and few detailed studies have been done, except for those by Doose and his coworkers [6–9,15,17,21,26,32]. One of the main values of syndrome classification is that it enables physicians to predict outcomes as well as select treatments specific for the syndrome. Especially since half of MAE patients have an unfavorable clinical course [8], it is crucial for clinical practice to identify better treatment strategies as well as the expected outcomes of this epileptic syndrome. The present study applied the international syndromic classification system to patients with childhood epilepsies consulting our clinic, identifying those fulfilling the definition of MAE, then retrospectively studied the response to treat-

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Received: December 28, 2001 · **Accepted after Revision:** March 4, 2002

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Neuropediatrics 2002; 33: 122–132 © Georg Thieme Verlag Stuttgart · New York · ISSN 0174-304X

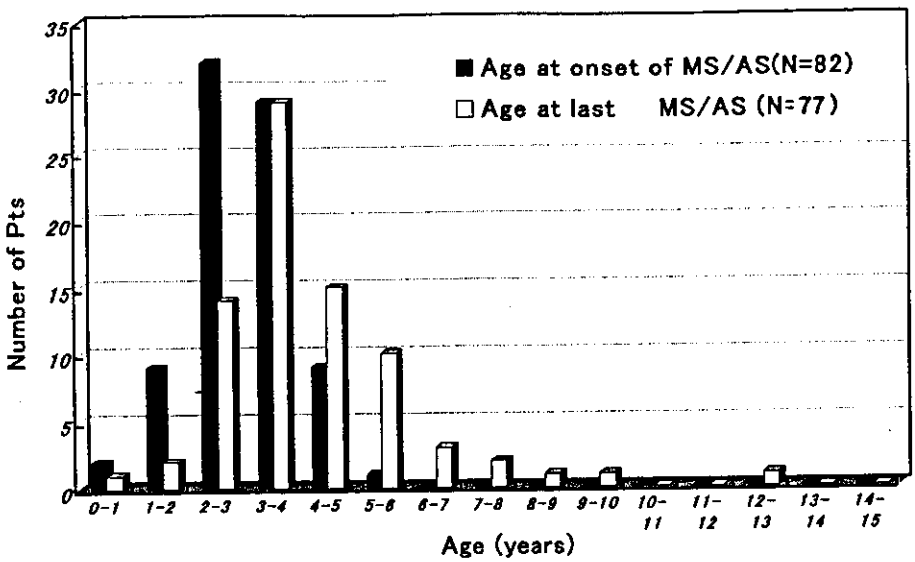

Fig. 1 Age at onset and last MS/AS. Age at onset of MS/AS, represented by black bar, scattered from 7 months to 5 years with a peak age at 2 to 4 years. Age at the last MS/AS represented by mesh bar scattered from 1 year to 12 years with a peak age at 2 to 6 years.

ment of myoclonic-astatic seizures and long-term mental development and seizure outcome.

Subjects

We recruited patients who fulfilled the criteria for MAE defined by the ILAE [34] from among 3600 patients registered in the database as having epilepsy. All of these patients had consulted our hospital between April 1968 and 1992. The ILAE criteria for MAE are as follows:

1. Normal development before onset of epilepsy and absence of organic cerebral abnormalities.
2. Onset of myoclonic, myoclonic-astatic seizures or astatic seizures (MS/AS) between 7 months and 6 years of age.
3. Presence of generalized spike- or polyspike-wave EEG discharges at 2–3 Hz, without focal spike discharges.
4. Follow-up for more than three years.
5. Exclusion of severe and benign myoclonic epilepsy in infants (SME, BME) as well as cryptogenic Lennox-Gastaut syndrome (LGS) based on ILAE definitions.

The exclusion of SME is mainly based on the clinical evolution lacking the following characteristics: the onset of epileptic seizures before the age of 1, repeated febrile or afebrile prolonged unilateral and generalized seizures, appearance of complex partial seizures after 1 year of age [31]. That of BME is mainly based on the presence of other seizure types than massive myoclonus, except for febrile convulsion [11]. Cryptogenic LGS is differentiated from MAE by the combination of generalized tonic seizures as a main seizure type during the early clinical course [3,13,29].

Methods

We retrospectively investigated clinical characteristics and evolution of MAE including seizure and intellectual prognosis, as well as responses to various medical treatments from the medical records. The seizure type was ascertained based on either the description given by surrounding adults including medical staff or on video-ictal EEG or polygraphic recordings. Routine EEG performed approximately every 6 months and ictal EEGs were also studied.

The effects of various antiepileptic drugs, ketogenic diet and ACTH treatments on the MS/AS, apparently a hallmark of this unique epileptic syndrome, were analyzed. Effectiveness of the treatments were according to the following criteria: Excellent: disappearance of MS/AS, Good: > 50% reduction of MS/AS, Poor: < 50% reduction of MS/AS, Aggravated: > 50% increase of MS/AS.

The intellectual outcome was evaluated on the basis of the intelligence quotient test (IQ test = Modified Binet IQ or WISC-R) and educational achievement for those patients with no available psychometric data. Patients were considered normal if IQ was over 80, borderline to mild if IQ was between 60 and 79, moderately retarded if IQ was between 30 and 59, and severely retarded if IQ was under 30.

By comparing the various clinical characteristics, we attempted to identify risk factors for poor seizure outcome capable of predicting the prognosis at the onset of MAE. χ^2-test or Fisher's exact probability test was used when n was less than 5 and ANOVA testing was used for comparisons. $P < 0.05$ was considered significant.

Results

Eighty-one patients fulfilling the criteria for MAE were included in this study. The follow-up period ranged from 36 to 320 months with a mean of 130 ± 73 months. There were more boys than girls by a ratio of 61: 20. Family histories of epilepsy (n = 11), febrile convulsions (FC, n = 15) and other seizures (n = 2) were seen in 28 patients accounting for 35% within 3rd degree relatives. Onset of epilepsy ranged from 6 months to 52 months of age with an average of 32 ± 9 months. Age at onset of MS/AS ranged from 7 to 63 months with a mean of 36 ± 11 months (Fig. 1). First seizure type other than MS/AS was always generalized tonic-clonic or clonic seizures [G(T)CS], seen in 63 patients or 78% of the patients. The interval between the first G(T)CS and the MS/AS ranged from 0 to 35 months with a median period of 1 month.

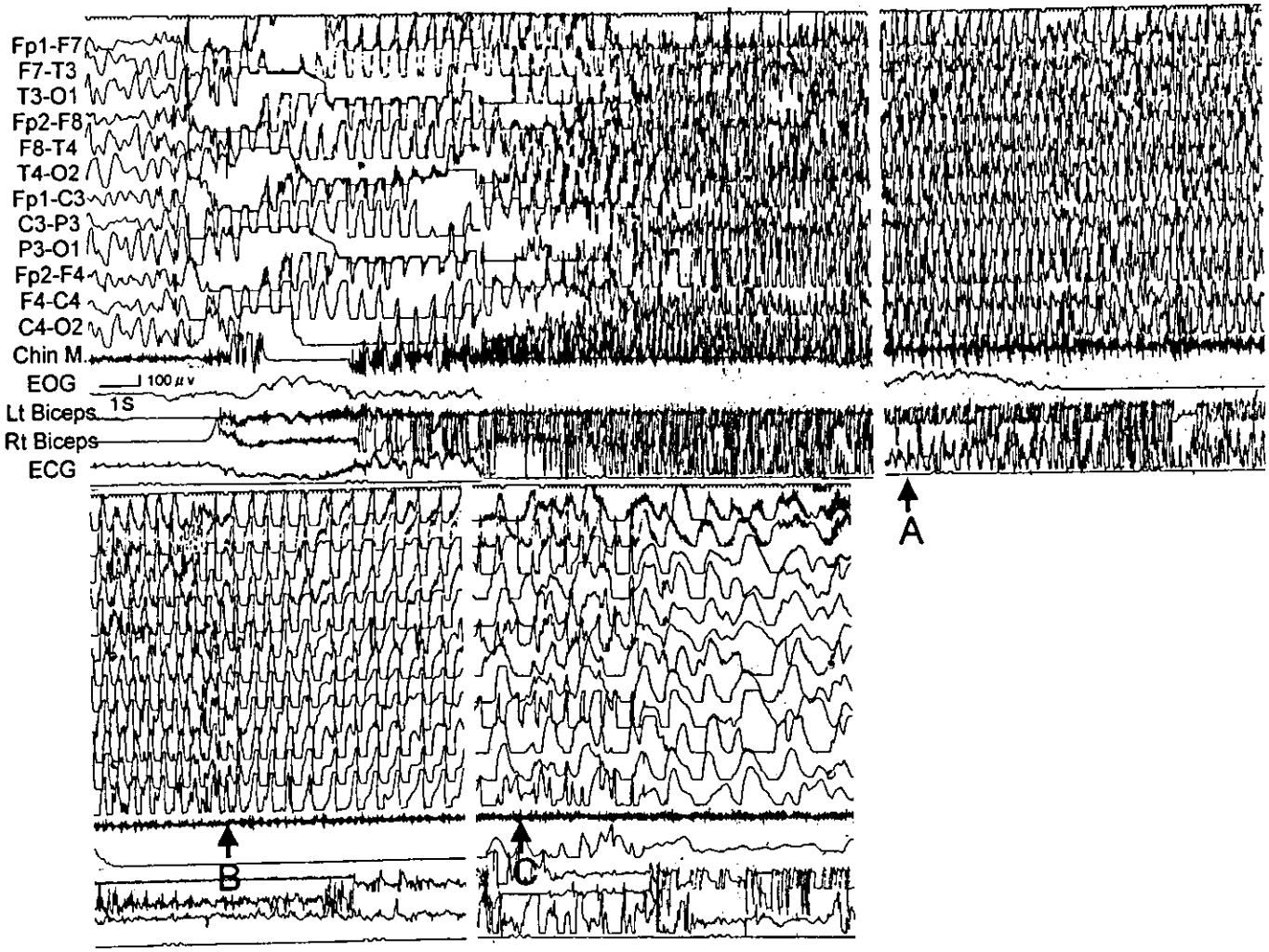

Fig. 2 Ictal simultaneous video-polygraph of generalized (tonic)-clonic seizures. **a** Generalized tonic-clonic seizures: The patient was a 3-year-old boy with favorable MAE (shown in Fig. **6**). During sleep, he suddenly developed GTCS, characterized by sudden extension of both arms and clonic jerks of the trunk several times followed by tonic-clonic activity lasting for 4 minutes. Ictal video showed diffuse clonic activity of the whole body with extension of both arms (A, starting video), which gradually became smaller (B), and terminated (C).

Clinical seizure manifestations

MS/AS was precisely investigated by video-EEG (n = 5), polygraph (n = 2) or video-polygraph (n = 22) in 29 patients. They consisted of myoclonic seizures in 17 cases, brief atonic seizures with or without preceding minor myoclonus in 11 cases and myoclonic-atonic seizures in 3 cases (3 cases had two seizure types). Although the type of MS/AS in the remaining 48 patients was assessed from the patients' history, seizure type analysis and long-term follow-up appeared to be reliable since 70% of patients were admitted to our hospital for detailed investigation of the epilepsy at the onset of epilepsy. Thirty-nine patients had astatic seizures, described as head-nodding attacks or drop attacks with immediate recovery and 18 patients had myoclonic seizures. Over all, drop attacks involving falling to the ground due to the seizure were recognized in 52 cases (64%) by either ictal monitoring or history. With respect to the seizure characteristics, myoclonic or atonic seizures occurred during waking in 70 cases or 86%, during sleep only in three each and in both the waking and sleeping state in the remaining 8. The attacks occurred daily in 57% of patients having less than 10 attacks per day, 31% having 10 to 50 attacks per day, and 12% having more than 50 attacks per day.

The most frequent accompanying seizures apart from MS/AS were G(T)CS seen in 75 patients (Fig. **2a**). Although it was difficult to estimate the exact number of patients, the brief GCS resembling the repetition of massive myoclonic attacks was clearly recognized. It was characterized by rhythmic opening of the mouth, arms and legs, suddenly collapsing backward on the floor and starting when the patient was sitting (Fig. **2b**). In 52 of 75 patients, G(T)CS occurred during both waking and sleep. Generalized tonic vibrating seizures with a few clonic components were confirmed in the later clinical course in those patients with unfavorable outcome (Fig. **3**). Atypical absence seizures corresponding to runs of generalized irregular spike-and-slow waves at 2–3 Hz were seen in 44 patients (Fig. **4a**). Eighteen of these patients also had recurrences of prolonged clouding of consciousness with random segmental myoclonus whose ictal EEG showed disorganized marked slow background activity with random spike and wave discharges, identical to the status of minor seizures or minor epileptic status (Figs. **4b, 4c**). This peculiar seizure tended to start after awakening from sleep and lasted for hours.

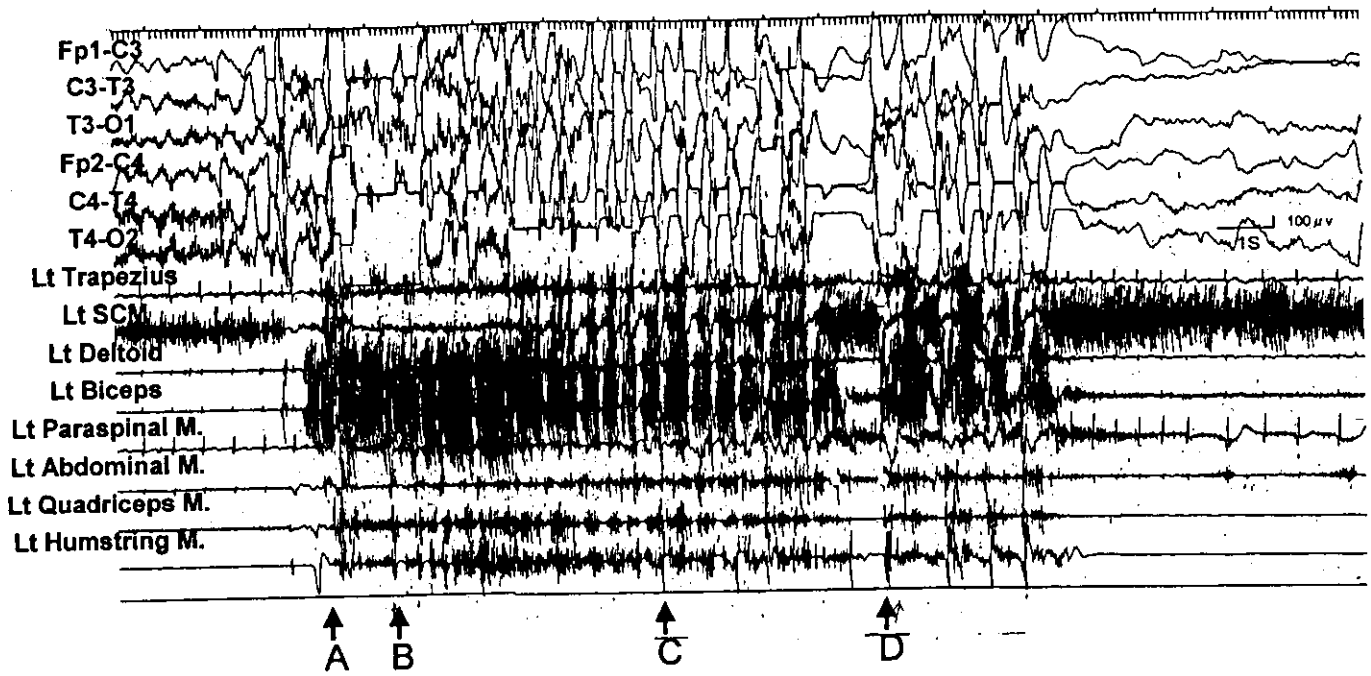

Fig. **2b** Generalized clonic seizures. The patient was a 4-year-7-month-old girl with unfavorable MAE. The polygraph showed sudden appearance of diffuse irregular spike-and-waves followed by EMG artifact and irregular rhythmic spike-and-slow discharges at 1–2 Hz lasting for 15 seconds. Ictal video showed that she suddenly extended both arms in front of her body, then fell backward (A) when she was sitting. This was immediately followed by clonic jerking of the trunk and both legs (B,C) as well as rhythmic opening of the mouth and finally by entire body movement at D.

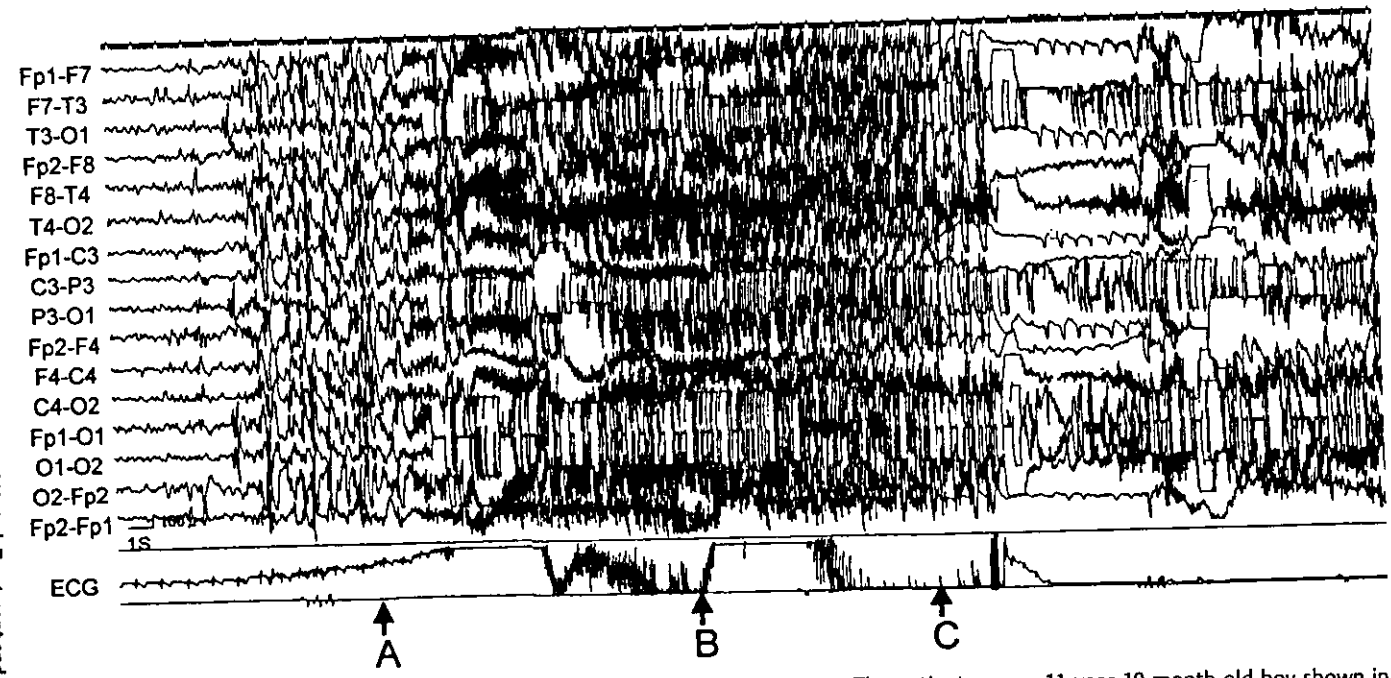

Fig. **3** Ictal simultaneous video-EEG of nocturnal generalized tonic vibrating seizure. The patient was an 11-year-10-month-old boy shown in Fig. 8. The EEG showed the sudden appearance of runs of generalized spike and waves followed by recruiting fast discharges, which were immediately obscured by EMG artifacts. In the ictal video, he showed gradual tonic flexion of both arms at A, then tonic extension of both arms at B, which vibrated incrementally and terminated with a few big jerks at C.

EEG findings

The MS/AS recorded in 33 patients including 4 with ictal EEG only corresponded to diffuse spike-and-waves or polyspikes-and-waves in all cases. Background activity during the active seizure period was evaluated in 72 children, of whom 66 children showed slowing of background activity consisting mainly of 4–7 Hz theta rhythm. The remaining 6 were considered to have normal background activity during the active seizure period. Photosensitivity was recorded in only 8 patients during late childhood.

Seizure outcomes

Age at last MS/AS ranged from 12 to 151 months with a mean of 51 ± 22 months and a median age of 46 m in 77 patients (Fig. **1**). The cumulative percent remission of MS/AS after the onset of

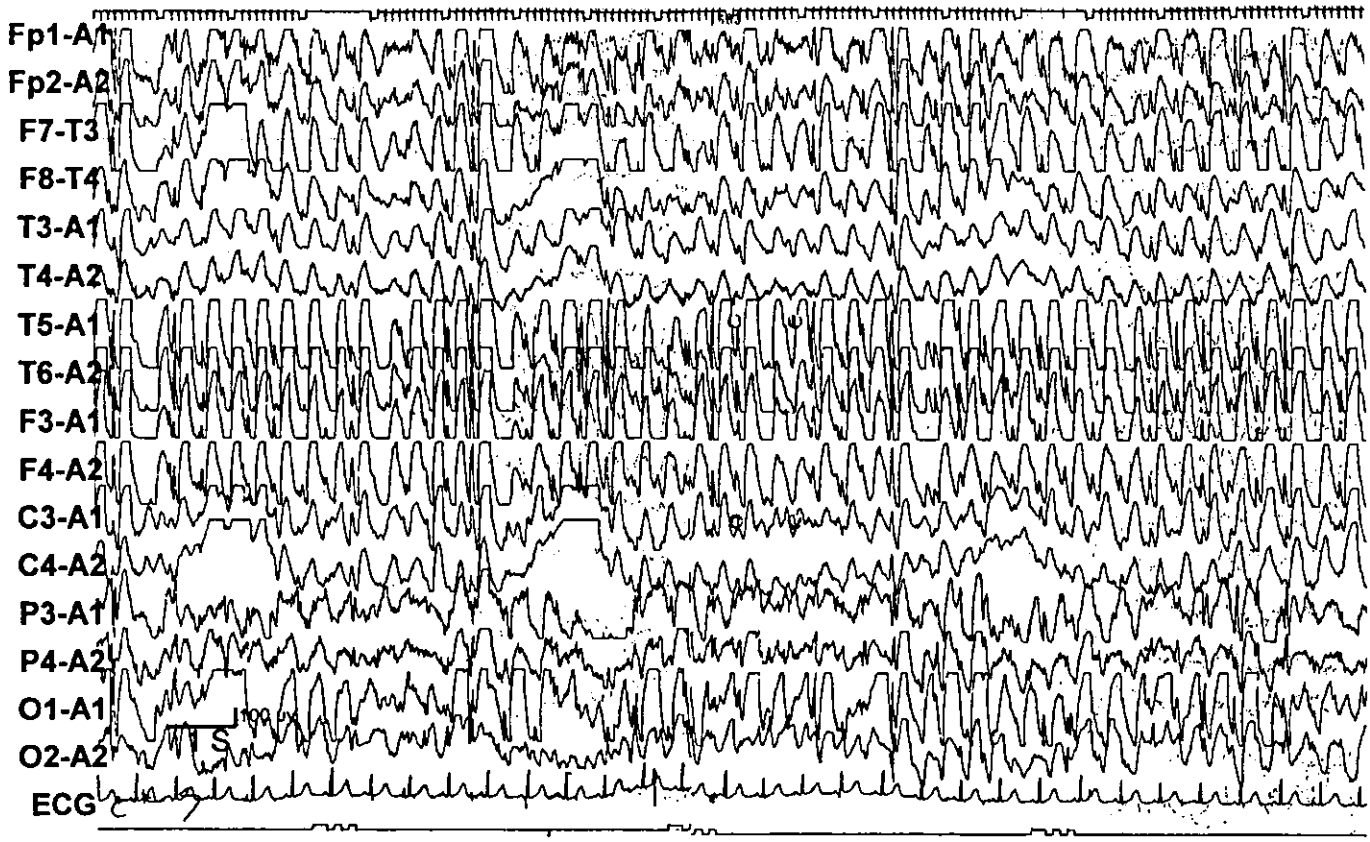

Fig. 4 Ictal EEG of atypical absence seizures and minor epileptic status. **a** Ictal EEG of atypical absence seizure. The patient was a 5-year-3-month-old girl with unfavorable MAE the same as the patient shown in Fig. 2B. EEG showed runs of generalized spike and waves at 2.5 Hz, corresponding to arrest of motion and unresponsiveness.

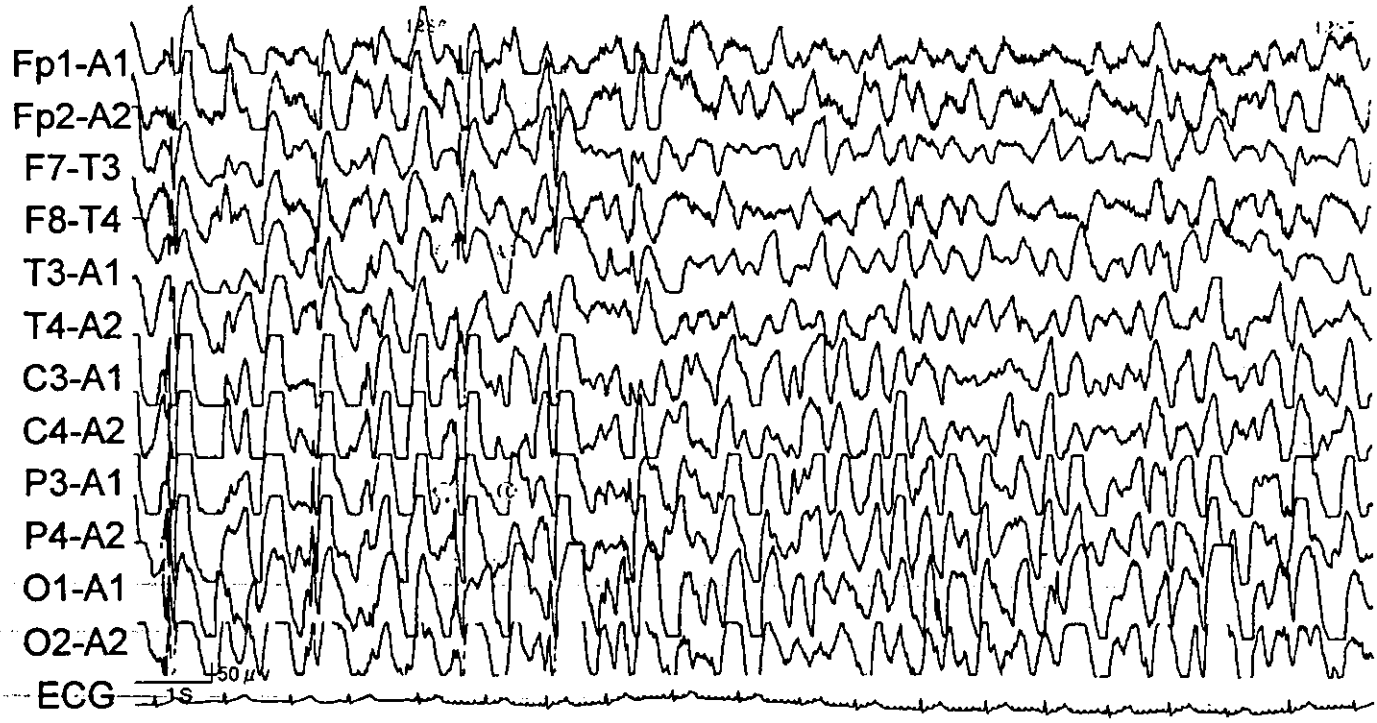

Fig. 4b Ictal EEGs of minor epileptic status. The patient was a 3-year-old boy with favorable MAE (shown in Fig. 6). EEG showed almost continuous high amplitude irregular slow wave discharges at times mixed with spike discharges, when the patient was sitting and listening to the story his mother was telling. He showed mild cloudiness of consciousness with occasional random myoclonus of the extremities.

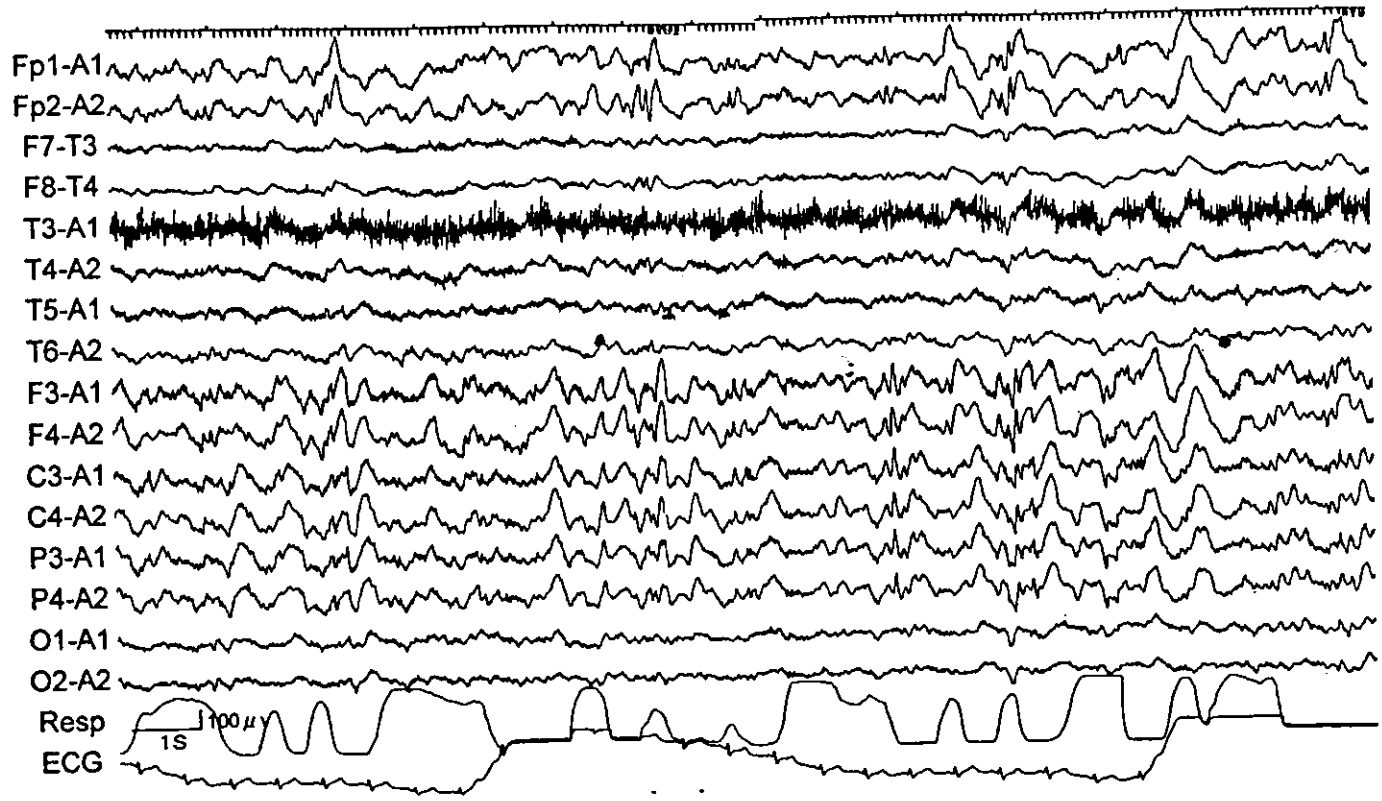

Fig. 4c Ictal EEGs of minor epileptic status. The patient was a 15-year-1-month-old boy with unfavorable MAE (shown in Fig. 8). He showed mild clouding of consciousness and reduced responsiveness corresponding to diffuse slowing background activity mixed with spike-and-wave discharge, lasting for hours after awakening.

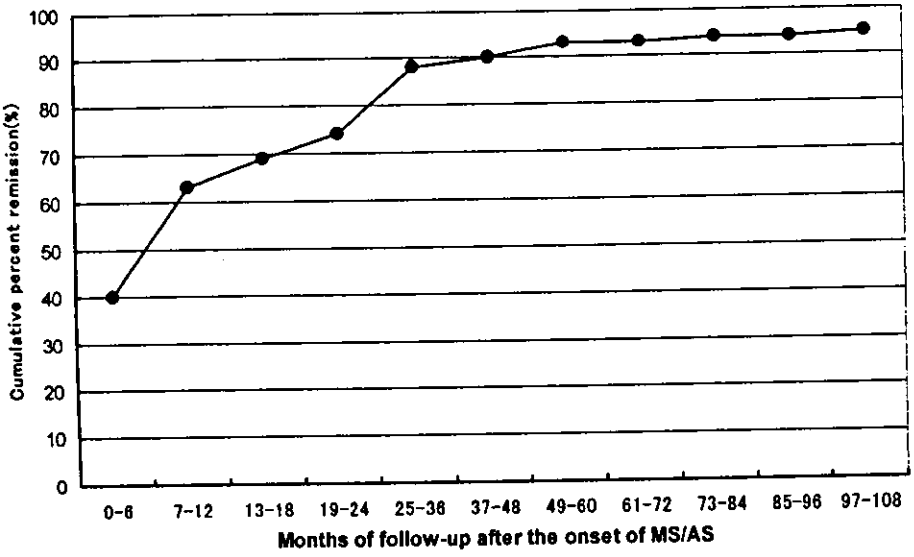

Fig. 5 Actual remission curve of myoclonic-astatic seizures for the 81 patients with MAE. Seventy-seven patients finally achieved remission of myoclonic-astatic seizures (seizure-free state for longer than 2 years). The most predominant seizures characterizing MAE despite initial resistance gradually disappeared or were controlled within 1 to 3 years from the onset.

the attacks was 40% within 6 months, 63% within one year and 89% within 3 years (Fig. 5). Minor epileptic status was also resistant but disappeared with MS/AS except in 5 patients with persistent nocturnal generalized tonic or tonic-clonic seizures. Thirty-five patients continued to have G(T)CS after remission of MS/AS. The remaining 4 patients had persistent MS/AS at the last follow-up. A seizure-free state longer than two years was attained in 55 patients or 68% of all patients by the age of 50 ± 16 months or a median age of 48 months. Remission of seizures appeared to be spontaneous in 21 patients, because the attacks disappeared suddenly or progressively without any change in medication. In 11 patients, or 14% overall, recurrence of GTCS was seen after a long remission period ranging from 3 years and 8 months to 17 years and 11 months with a mean of 9 years and 2 months ± 4 years and 4 months. However, GTCS were controlled easily by reinstitution or increase of the dose of AED. Finally, the remaining 15 patients or 18% continued to have frequent attacks. Seven patients had weekly nocturnal generalized tonic or tonic-clonic seizures, and minor epileptic status resistant to the currently available AEDs. Five patients continued to have weekly GTCS only. Two patients continued to have daily myoclonic seizures at the final examination. The remaining patient continued to have complex partial seizures of frontal origin, which have developed since age 18 years, long after remission of myoclonic seizures.

Intellectual outcome

As to the intellectual outcomes, 48 patients or 59% of all the patients showed a normal IQ level at the final follow-up, 16 patients or 20% were borderline or had mild retardation, and 17 patients or 21% had less than moderate retardation, respectively. The 17 patients with less than moderate retardation continued to have seizures at the final follow-up.

Responses to the various antiepileptic drugs

Antiepileptic drugs (AEDs) including valproic acid (VPA), ethosuximide (ESM), clonazepam (CZP), nitrazepam (NTZ), ACTH and ketogenic diet were most frequently employed to control MS/AS. VPA, CZP, NTZ and ESM were either introduced individually or added to the preexisting drug regimen in 57, 43, 36 and 34 patients, respectively (Table **1**). Among these therapies, ketogenic diet treatment with either classical or MCT types, followed by ACTH, ESM, CZP, VPA and NTZ in this order was most effective, exhibiting excellent effects in 58% of the patients. Among the AEDs, ESM was the most effective inducing a good or better response in 64% of the patients, achieving results almost comparable with those of ACTH. Although the response to treatments for other seizure types was difficult to evaluate, ketogenic diet treatment also appeared to be effective for convulsive and non-convulsive seizures.

Table **1** Effectiveness of the various treatments for MS/AS

AEDs	*Excellent*	*Good*	*Poor*	*Aggravated*	*Total*
KD	15 (58)	9 (35)	2 (7)	0	26
ACTH	8 (36)	5 (23)	8 (36)	1 (5)	22
ESM	11 (32)	11 (32)	12 (36)	0	34
CZP	6 (14)	10 (23)	25 (58)	2 (5)	43
VPA	7 (12)	16 (28)	34 (60)	0	57
NTZ	1 (3)	7 (19)	28 (78)	0	36
Total	48	58	109	3	218

KD = Ketogenic diet, () indicated % of effectiveness.

Identifying factors that predict an unfavorable prognosis

The following clinical findings were compared among 55 patients with a favorable prognosis, 11 patients with an intermediate prognosis (recurrences of GTCS after a long remission period and requiring medication) and 15 patients with unfavorable outcomes: the age at onset of epilepsy, the age at onset of MS/AS, incidences of nocturnal seizures, atypical absence seizures, absence status or minor epileptic status, combination of drop attacks and incidence of family histories of epilepsy and febrile convulsions (Table **2**). There was a significant difference in positive family history of epilepsy and incidence of absence status or minor epileptic status ($p < 0.05$).

Representative Cases

Case 1 was a 15-year-3-month-old boy with a favorable outcome (Fig. **6**). He first developed GTCS at the age of 2 years and 3 months. Subsequently, he had recurrent GTCS and atonic drop attacks every day. He sometimes showed a prolonged mild cloudiness with random myoclonus diagnosed as minor epileptic status (Fig. **4b**). As VPA in combination with ESM was not effective, ACTH treatment was initiated at the age of 3 years. The attacks were controlled immediately except for nocturnal GTCS, which gradually disappeared within a few months (Fig. **2a**). He has been seizure-free for more than 12 years and his IQ was 103 at the last follow-up.

Case 2 was a 21-year-7-month-old man with intermediate outcome (Fig. **7**). He developed a febrile convulsion followed by recurrence of afebrile GTCS at age 3 years. Within a few months, astatic seizures including head dropping or collapsing of the body occurred every day, and were resistant to AEDs. ACTH and

Table **2** A comparison of the various clinical factors among three groups with different outcomes

Outcomes	*Favorable*	*Intermediate*	*Unfavorable*		*P*
N	55	11	15		
Boy/Girl	41/14	10/1	10/5		0.3571
Age onset of epilepsy (m)	33±8	32±9	30±11		0.4502
Age onset of MS/AS (m)	36±9	37±14	35±14		0.9878
FH of Epilepsy + FC	4+11	1+2	6+2	*Epi*	***0.0108***
				FC	0.8403
				Epi + FC	0.1489
Seizure type					
Absence	27 (49%)	6 (55%)	10 (67%)		0.4789
Absence status or MES	9 (16%)	1 (9%)	7 (47%)		***0.0222***
			Favorable vs. Intermediate		0.8887
			Favorable vs. Unfavorable		***0.0132***
			Intermediate vs. Unfavorable		0.1050
Nocturnal seizures	34 (62%)	8 (73%)	10 (67%)		0.7697
Drop attacks	35 (64%)	7 (64%)	10 (67%)		0.9759

Abbreviations: MS/AS = Myoclonic or atonic seizures, FH = Family history, FC = Febrile convulsions, MES = Minor epileptic status, Epi = Epilepsy

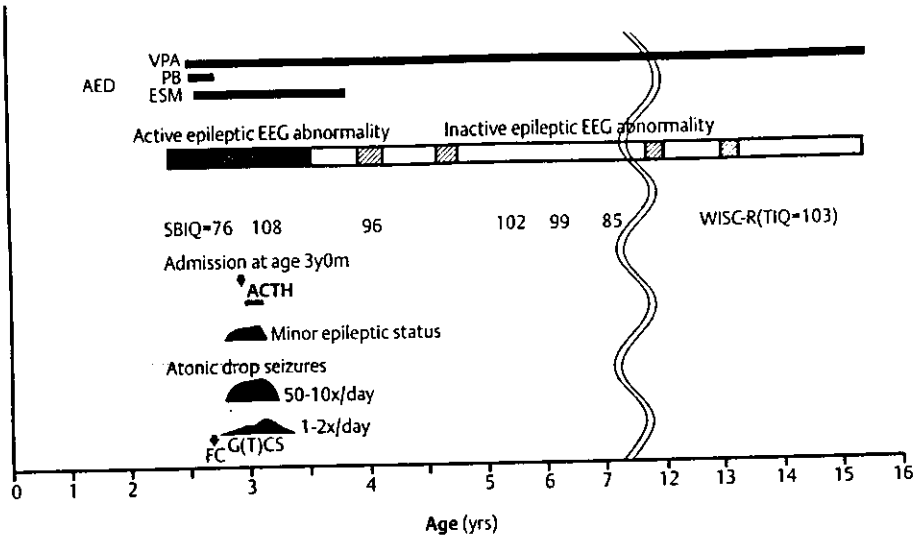

Fig. 6 Clinical evolution of a 15-year-3-month-old boy with favorable MAE. Abbreviation: dense oblique line = active epileptic EEG abnormality, oblique line = inactive epileptic abnormality, FC = Febrile convulsion, G(T)CS = generalized tonic-clonic seizures or generalized clonic seizures.

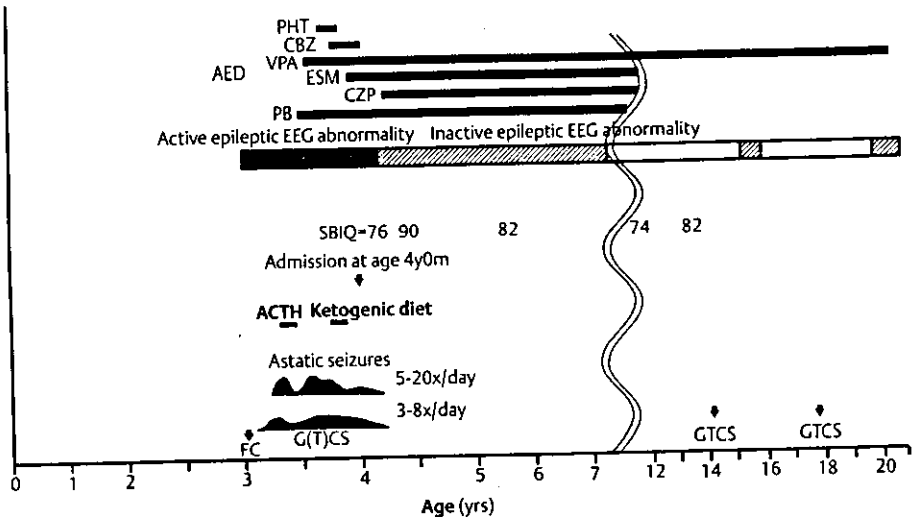

Fig. 7 Clinical evolution of a 21-year-7-month-old boy with intermediate outcome. Abbreviations are the same as those in Fig. 6.

ketogenic diet were only partially effective. However, all attacks gradually disappeared without any particular effect of AEDs. GTCS recurred after a long-remission period when he did not take VPA for one day at age 14 years and 1 month and again at 17 years and 10 months.

Case 3 was a 17-year-10-month-old boy with unfavorable outcome (Fig. 8). He started to have GTCS at the age of 4 years and 2 months. Atonic drop attacks and atypical absence seizures developed subsequently. Although all the available AEDs were not effective, ketogenic diet treatment controlled atonic drop attacks and reduced the number of the remaining attacks. However, subsequently, nocturnal generalized tonic seizures and minor epileptic status persisted and remained uncontrolled until the last follow-up, leaving the patient moderately retarded (Figs. 3, 4c).

Discussion

There have been several distinct studies and reviews regarding cryptogenic or idiopathic myoclonic epilepsies during childhood since the first description by Harper who reported 14 children with true myoclonic epilepsy [18]. Harper previously described an astatic symptomatology that often followed violent myoclonic attacks, and was often resistant to antiepileptic drugs (AEDs). Then Doose reported the detailed analysis of 50 children with so-called centrencepahlic myoclonic-astatic petit mal [6], later designated as myoclonic-astatic epilepsy [8,9]. In the following years, Aicardi et al studied children with predominantly myoclonic seizures and classified those without permanent neurological signs into myoclonic-petit mal, petit-mal variant with myoclonic jerks, generalized epilepsy with myoclonic jerks and cryptogenic myoclonic epilepsy of childhood according to a detailed study of the clinical and EEG features [1]. Subsequently, various authors have proposed various terminologies describing those with similar features: intermediate cryptogenic myoclonic epilepsy of childhood because of clinical and EEG characteristics between idiopathic and symptomatic etiology [35], myoclonic variant of Lennox-Gastaut syndrome (LGS) because of the combination of atypical absence seizures or status, and slow-spike-and-wave complexes activated by sleep sharing the features of LGS [1,10,35]. Dravet et al finally established benign myoclonic epilepsy in infants (BME) [11] and severe myoclonic epilepsy in infants (SME) [12] as distinct epileptic syndromes, both of which are accepted by ILAE along with MAE proposed by Doose [34].

However, as Aicardi pointed out, the nosological confusion has remained unsolved because of the subdivision of these epilepsies

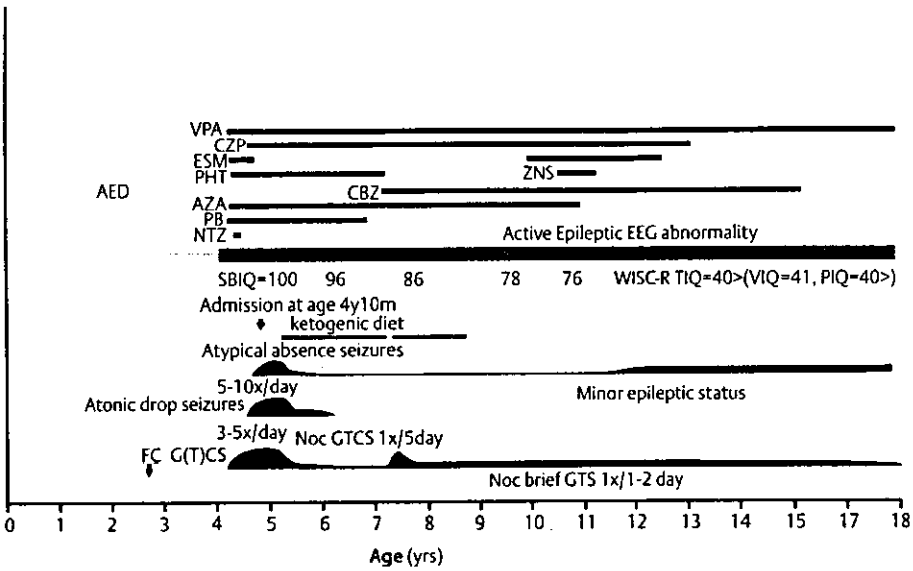

Fig. 8 Clinical evolution of a 17-year-10-month-old boy with unfavorable MAE. Abbreviation: Noc GCS = nocturnal generalized clonic seizures.

by different methodologies based on the clinical and EEG features or on the etiology [4]. In his latest publication, Aicardi himself attempts to formulate a concept in which these heterogeneous myoclonic epilepsies of childhood and cryptogenic LGS form a spectrum with LGS at the malignant end and BME at the benign end, with the myoclonic variant of LGS and MAE or other cryptogenic myoclonic epilepsies existing at intermediate points along the continuum [4]. In our previous studies, we reached a similar conclusion that 60 children with cryptogenic or idiopathic myoclonic epilepsies and ultimately favorable outcomes appeared to form a clinical continuum with respect to seizure and intellectual outcomes that depended largely on the persistence of nocturnal G(T)CS rather than on MS/AS [24,25]. However, we favored considering these patients as representing one clinical entity with a rather wide clinical spectrum than as an assemblage of heterogeneous epilepsies after excluding SME.

Most authors have claimed that MAE is merely a group of heterogeneous epileptic syndromes and should be limited to those involving myoclonic-astatic seizures or astatic seizures [4,10,15, 17,21,35]. However, Doose himself has resisted the separation of MAE by clinico-electrical features into many overlapping subdivisions [8,9]. As to the etiology of MAE, Doose and Baier extensively studied the convulsive trait in families of MAE patients and demonstrated the pathogenic importance of multifactorial inheritance of this type of epilepsy [7]. They concluded that the neurobiological approach for MAE would provide a clue to the ultimate understanding of the pathogenesis of MAE rather than sticking to the rigidly defined syndromatic classification. Recent advances in molecular biology have come to shed light on his concept and are providing more concrete evidence [38].

With respect to the characteristic symptomatology of the myoclonic/astatic seizure (MS/AS) itself, the recent advent of video-EEG monitoring system has clarified differences in these brief events very precisely. As we have already shown, drop attacks in MAE consisted either of brief atonic seizure with or without preceding minor myoclonic events or flexor spasm both associated with generalized spike-and-wave [26,27,30,32]. Thus, the astatic symptomatology itself created by the heterogeneous seizure types does not appear to be an appropriate indicator for subdividing the epileptic syndromes [32]. In addition, we should pay more attention to the evidence that tonic drop attacks, a hallmark of LGS, appear to be more common than atonic attacks [16,19]. Thus, the exclusion of cryptogenic LGS may not be easier unless we carefully evaluate drop attacks by taking a detailed seizure history or by ictal video-polygraphic study.

Guerrini et al as well as Dulac et al have proposed that MAE should be limited to those with massive myoclonic or drop attacks with or without absence or GTCS excluding BME, SME and cryptogenic LGS [15,17]. Most recently, Kaminska et al have justified their subdivision into favorable and unfavorable MAE by multiple corresponding analysis [21]. In this study, we recruited patients according to the ILAE defined criteria of MAE, excluding those with BME, SME and cryptogenic LGS. Thus, our series may include heterogeneous epileptic syndromes, which are of concern to some investigators, but at least excluded other ILAE defined subgroups similar to their concept.

In comparison with nosological issues described above, only a few detailed studies have been performed concerning the long-term prognosis and treatment of MAE [17,21,32]. Doose has recommended the combination of valproic acid and ethosuximide for MS/AS and primidone for GTCS [8]. In addition, he used ACTH to treat minor epileptic status. He has also suggested the use of bromide for the severe form of MAE, which shows clinical characteristics identical to those of SME [28]. Most other authors more or less described MS/AS as relatively resistant to therapy but did not include further details of the treatment other than those Doose recommended [2,4,10,17,18,21,35,40]. Despite being a retrospective study, the present results showed that MS/AS were initially resistant to conventional AEDs commonly recommended for myoclonic seizures and atonic seizures. However, Doose as well as other investigators suggested that ethosuximide appeared to be the most favorable AED for the MS/AS, although it was difficult to assess whether a combination with VPA was better [4,8,40]. The combination of ESM with VPA has been reported to be effective for refractory absence seizures [37] and considered to have a synergic effect on absence seizures or bursts of spike-and-wave complexes. In our previous studies as well as the present ictal EEG series of MS/AS, these attacks all corre-

sponded to generalized spike-and-wave complexes, similar in part to the ictal EEG of absence seizures despite differences in frequency and duration [26,27,30,32]. The much better responses to ACTH and ketogenic diet than to ESM could be due to the same reason, because both treatments have been shown to be most effective for atypical absence seizures and myoclonic seizures but not so effective for generalized tonic seizures which are rare in MAE [39,41]. Recently, lamotrigine has been successfully tried for some MAE patients [14], although we have no experience to treat MAE with this drug.

As for seizure outcomes, it is evident that the prognosis of MAE in our series is clearly better than that demonstrated by Doose [8,9], probably because of the exclusion of SME. In the clinical course, we tentatively separated patients into three groups, favorable, intermediate and unfavorable outcomes, according to the seizure prognosis. However, we should keep in mind that even in those with a favorable clinical course, the attacks were initially resistant to the AEDs, sometimes requiring additional ACTH or ketogenic treatment as shown in the case reported above. The patients with an unfavorable outcome appeared to be identical to those reported by Kaminska et al [21], characterized by a combination of MA/AS, atypical absence seizures, minor epileptic status and recurrent GTCS at the early clinical course, although later accompanied by nocturnal GTCS or GTS. The course of patients with an intermediate outcome resembled that of those with BME to some extent, experiencing recurrences of GTCS after long remission periods [11].

With respect to the prognosis of the MS/AS, a hallmark of MAE, they ultimately disappeared within 1 to 3 years after onset. Minor epileptic status was also resistant but two thirds of them disappeared with MS/AS. However, generalized convulsive seizures tended to continue, especially during sleep after disappearance of the MS/AS. Nocturnal attacks gradually disappeared and only 18% of those finally became truly intractable. Half of those with an unfavorable outcome were characterized by a combination of weekly brief nocturnal GTS and daily or weekly minor epileptic status, persisting for years, being left with moderate to severe mental retardation. The clinical characteristics appeared to be different from those of cryptogenic LGS because this seizure combination was consistent in MAE with an unfavorable outcome.

Doose himself identified the following risk factors for an unfavorable prognosis: onset with febrile and afebrile GTCS during the first and second year of life, status of minor seizures, and tonic seizures, the persistence of 4–7 Hz rhythms until adolescence and adulthood, and failure to develop a stable occipital alpha rhythm [9]. In our series, we confirmed that the family history of epilepsy and the combination of minor epileptic status were significantly higher in incidences in the unfavorable group. The other authors also indicated the following risk factors: the presence of epileptic seizures prior to myoclonic seizures, abnormal mental development antecedent to myoclonia, the lack of familial antecedents, the presence of tonic and absence seizures, persistence of epilepsy over 3 years, vibrating tonic seizures and the occurrence of myoclonic status [2,21]. However, further prospective study is necessary to confirm which risk factors can legitimately predict the outcome.

During the clinical follow-up of MAE, we noticed the apparent spontaneous remission of the attacks without changing medications in 21 cases as Doose also indicated [8,9]. In some cases, there was a sudden disappearance of attacks while, in other cases disappearance was gradual. In that sense, the response to treatment appeared to also be influenced by the timing of treatment, as the response was poor at the peak of the epileptic condition, then later improved as shown by the increased remission rate over time in patients with favorable and intermediate outcomes.

The concept of MAE still contains some nosological problems and it may be difficult to reach a conclusion as long as we depend largely on clinico-electrical manifestations to classify the epilepsies. Precise resolution of nosological issues may await the further development of molecular biological analysis. However, from a practical perspective, we are able to determine the appropriate treatment strategy and to predict the prognosis more accurately. At present, MAE should be recognized as an epileptic syndrome with a relatively wide clinical spectrum ranging in its main seizure type from myoclonic to atonic attacks, and in the seizure and intellectual outcomes from favorable to unfavorable. However, the final prognosis in most patients with MAE, despite the initial resistance, appears to be better when we follow ILAE definitions excluding SME from the original MAE series.

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III．けいれん・意識障害を起こす疾患の診療のポイント

4．脳梗塞の診療のポイント

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Key words：脳梗塞，脳浮腫，脳循環

脳梗塞は，さまざまな原因で脳動脈の血流障害が一過性あるいは持続性に起こり，その支配領域の脳組織が虚血性壊死に陥る疾患である。小児期の脳梗塞は成人に比してまれで，その頻度は10万人に約0.2～1.2人であるが，胎生期，周産期を含め，小児のあらゆる時期に発症する。発症機序は，血栓性，塞栓性，血行力学性に分類される。脳梗塞の診断，治療を進めていくうえで，脳虚血に伴う病態生理を概説する。虚血に陥った神経細胞は急速にATPを失い，膜脱分極をきたし，シナプスからグルタミン酸が放出され，Caチャンネルを通して，細胞内にNa^+，Ca^+の流入が起こり細胞性浮腫（cytotoxic edema）を生じる。さらに，発症数時間後に血液脳関門の障害から，血管外へ血漿蛋白が漏出して細胞外液腔の浸透圧が上昇し浮腫が増強する（vasogenic edema）。脳浮腫は発症3～5日ごろが最大で，1週間後まで持続する（急性期）。発症1週以降，脳浮腫は次第に改善し（吸収期），発症1～3か月までにグリア細胞に置換され瘢痕化する（慢性期）。

【症状・診察所見のポイント】

急激に意識障害，片麻痺，けいれんなどの神経症状を呈する病態をみた場合，まず意識レベル，呼吸，脈拍，血圧，体温などのvital signの把握が重要である。問診で，発作の起こり方（前駆症状なく急激な発症，反復性の発作など），誘因（過呼吸，感染，脱水，外傷，医療的処置など），基礎疾患（心疾患，膠原病，血液疾患，代謝疾患など）を家族，本人，搬送者から聴取し，一般理学的診察を行う。脳梗塞に加え，脳虚血をきたす病因を表1に示す。

脳梗塞急性期の神経学的症候として，意識障害，失語・失行・失書・失算・失読・指失認などの高次脳機能障害，けいれん，1肢または上下肢の協調運動障害や脱力（麻痺），構音障害，視力・視野障害，知覚障害，失調，めまい，嘔吐，悪心，頭痛などの評価を行う。重症例では，脳浮腫の程度，肺炎，尿路感染などの合併症のチェックも必要である。典型的な神経症状がそろえば，障害された脳動脈（内頸動脈，前・中・後大脳動脈，脳底動脈）の推定が可能である。しかし，多くの成人における血管障害で出現するこれらの臨床症状とは異なり，小児の場合には，しばしばけいれん，発熱，ぐったりしだしたといった非特異的症状を呈するために，脳梗塞の疑いをもつことが容易でないことがしばしば経験される。したがって，問診，診察を通して，脳梗塞を疑うことが肝要である。

【検査の進め方のポイント】

脳梗塞急性期における緊急検査を表2に示す。画像検査を進めていくうえで，CTおよびMRI撮像各シーケンスの特徴を表3に示す。急性期の画像診断は，まず短時間で施行できるCTを行うが，発症6時間以内では変化が認められない。超急性期梗塞（発症1～3時間）の診断には，細胞性浮腫による拡散低下により高信号を呈する拡散強調画像が最も有用な検査法である。さらに，頭蓋内外の動脈の描出にMR angiographyやtrans-

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表 1　脳梗塞，脳虚血をきたす疾患

1）心臓疾患
　先天性心疾患，リウマチ性心疾患，心内膜症，心筋炎，心房粘液腫，心筋症，心筋梗塞，不整脈，弁置換術など
2）血管形成異常
　もやもや病，線維筋性異形成症，神経線維腫症，血管奇形，結節性硬化症，Sturge-Weber 症候群，Down 症候群など
3）結合織病
　弾力線維性偽黄色腫，Ehlers-Danlos 症候群，Marfan 症候群など
4）全身の血管・血行異常
　循環不全，脱水，血圧低下，高 Na 血症，糖尿病，高脂血症，動脈硬化症（progeria など）
5）血管炎
　髄膜炎（結核，インフルエンザ菌，ウイルス），扁桃炎，静脈洞血栓症，膠原病（SLE，高安病，結節性動脈周囲炎），川崎病，アレルギー性紫斑病，大動脈炎症候群，水痘，マイコプラズマ，ムンプス，薬剤性など
6）血液・凝固異常
　ヘモグロビン異常（鎌状赤血球性貧血など），多血症，血小板増多症，白血病，DIC，HUS，TTP，高リン脂質抗体症候群，アンチトロンビンIII欠損症，プロテインC欠損症，プロテインS欠損症など
7）代謝異常
　ミトコンドリア脳筋症（MELAS など），ホモシスチン尿症，メチルマロン酸血症，OTC 欠損症，Menkes 病など
8）外傷
　口腔内損傷（pencil injury など），頭部鈍的外傷，脂肪・空気塞栓など
9）脳血管攣縮
　片頭痛，交代性片麻痺，クモ膜下出血後など
10）その他
　晩期放射線障害，動脈カテーテル操作，胎盤塞栓，双胎間輸血症候群，薬剤性（L-アスパラギナーゼなど）

表 2　脳梗塞急性期における緊急検査

1）一般血液検査（血算，電解質，生化学，血糖，凝固系，CRP など）
2）動脈血ガス分析
3）髄液検査（正常 CT を確認して）
4）胸部 X 線
5）心電図
6）頭部 CT
7）脳波（けいれん出現あるいは疑いのあるとき）

表 3　脳梗塞における CT，MRI 所見の特徴

CT
　脳浮腫が進行するにつれ低吸収域となるが，発症後 12 時間以内は異常は検出できないことが多い。
MRI
　拡散強調像
　　細胞性浮腫によるプロトン拡散の低下により脳梗塞超急性期（発症後1～3時間）の診断に有用。
　T_2強調像
　　急性期の診断には必須の撮像シーケンス。正常血流のある動脈内腔は flow void（無信号）のため，閉塞した動脈内腔は flow void の消失が認められる。
　FLAIR 法
　　脳脊髄液の信号を抑制した T_2強調像で，皮質や脳室周囲の小梗塞の検出に有用。
　プロトン密度強調像
　　急性期の静脈洞・深部静脈血栓における診断に本法の flow void の消失が有用。
　T_1強調像
　　出血や血栓の経時的変化の診断に有用。
　造影 T_1強調像
　　梗塞と腫瘍病変の鑑別，側副血流の程度，動脈内腔の精査に有用。

表 4　脳梗塞の基礎疾患に対する検査項目

1）心疾患
　心電図，心エコー検査，CK
2）血管炎
　抗核抗体，抗 DNA 抗体，補体，RA，β_2ミクログロブリン，フェリチン，各種細菌，ウイルス検査
3）血液・凝固異常
　PT，APTT，TAT，フィブリノーゲン，トロンボテスト，FDP，D ダイマー，プロテイン C，プロテイン S，ループスアンチコアグラント，抗カルジオリピン抗体，アンチトロンビンIII
4）代謝異常
　乳酸・ピルビン酸（含，髄液），アミノ酸分析

cranial doppler sonography を行う。ついで，治療計画や生命機能予後を推定するため，局所脳血流を SPECT などの脳循環検査で評価する。必要に応じて，脳波，髄液検査，脳血管造影を行う。同時に，脳梗塞の原因となる基礎疾患に対する検査を行うが，その検査項目を表 4 に示す。

【診断・鑑別診断のポイント】

脳梗塞は，誘因，発作の起こり方，基礎疾患などの病歴の聴取，理学的・神経学的所見，動脈支

表 5　脳梗塞の治療

1）急性期一般的治療
　a）救急処置
　　気道確保，酸素マスク，人工換気，血圧管理，輸液療法，尿道バルーンカテーテル
　b）けいれん
　　ジアゼパム，リドカイン（フェニトイン），ミダゾラム，ネンブタールを適宜使用
　c）脳浮腫
　　10%グリセオール，デキサメサゾン
　d）感染
　　抗生物質
　e）消化管出血
　　抗潰瘍薬，制酸剤
2）急性期特殊治療
　a）血栓溶解療法
　　ウロキナーゼ（成人のみ適応で発症 5 日以内に1日 6 万単位を 7 日間点滴静注，出血性梗塞の合併に注意）
　b）抗凝固・抗血小板療法
　　ヘパリン（初回 30～50 単位/kg 静注し，200～500 単位/kg/日で維持，脳塞栓が適応，出血の合併に注意），アスピリン（成人では発症 2 日以内に 160～300 mg/日投与して，再発予防に使用，小児ではアスピリン 1～5 mg/kg/日経口投与），オザクレルナトリウム（成人では発症 3 日以内に 2 次血栓形成阻止の目的で，160 mg/日を 2 週間点滴静注）
　c）血液粘度亢進の改善
　　低分子デキストラン（10 ml/kg/日以下を持続点滴，心負荷，脳浮腫の助長に注意）
　d）低体温療法
　　人工呼吸器，冷却用マットなどを使用して脳温を 33℃まで下降させ，3 日間維持，本法は脳梗塞ではスタンダードな方法ではないが超急性期脳塞栓症で有用性が報告されている。
3）慢性期治療
　a）抗血小板・抗凝固療法
　　アスピリン，チクロピジン（3～5 mg/kg/日），ワーファリン（0.1～0.2 mg/kg/日，心原性に使用される）
　b）脳循環・代謝改善薬
　　脳血管拡張，脳代謝改善，抗血小板作用のある薬剤が使用される。
　c）リハビリテーション
　　理学・作業・言語・心理療法を早期に開始

配領域に一致した病変の広がりと経時的変化を認める画像所見から，ほぼ診断は可能である。鑑別診断には，びまん性に浸潤する脳腫瘍（神経膠腫や悪性リンパ腫など），病変周囲の浮腫（外傷，脳炎，脳膿瘍など），脱髄疾患（多発性硬化症，ADEM など），同じ虚血性疾患ではあるが，膠原病，ミトコンドリア脳筋症，片頭痛などがあげられる。

【治療のポイント】

治療は，脳梗塞の原因が明らかな場合は，その基礎疾患の治療を行う。脳梗塞の急性期治療は，全身状態の管理を中心とする救急処置と脳循環改善を目的とする特殊治療（閉塞した脳血管を再開通させる血栓溶解療法，血栓の進展を阻止する抗凝固療法，抗血小板療法，虚血による神経細胞や微小循環の障害を軽減する目的で行われる低体温療法），さらに再発の予防を目的として慢性期治療を行う（表 5）。臥床期から良性位保持に努め，早期に理学療法，言語療法，作業療法を行う。

Epilepsia, 43(9):1039–1048, 2002
Blackwell Publishing, Inc.

Quantitative Analysis of Benzodiazepine Receptor in Temporal Lobe Epilepsy: [^{125}I]Iomazenil Autoradiographic Study of Surgically Resected Specimens

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Summary: *Purpose:* To evaluate the changes of the inhibitory neurotransmitter receptor system related to epileptogenesis by measuring central benzodiazepine receptors (BZDRs) in surgically resected specimens of temporal lobe epilepsy by using [^{125}I]iomazenil autoradiography.

Methods: Surgically resected specimens were obtained from 66 temporal lobe epilepsy patients [51 with mesial temporal lobe epilepsy (MTLE) and 15 with non-MTLE] receiving no BZDs and seven MTLE patients receiving BZDs. BZDR densities in brain sections were measured by using [^{125}I]iomazenil autoradiography. Cell densities were measured from cresyl violet–stained sections.

Results: Compared with non-MTLE patients, non–BZD-treated MTLE patients showed remarkable reduction of BZDR density in the pyramidal cell region of cornu ammonis (CA) 1, CA3, and CA4, and a smaller but significant reduction in CA2 and the molecular and granule cell layers of dentate gyrus (mDG). In the MTLE group, the BZDR density in the mDG correlated with that in lateral cortex. Significant correlations between BZDR density and cell density were found in all hippocampal regions. A significant difference in BZDR density/cell-density ratio was observed in CA1 region between MTLE and non-MTLE. BZD-treated patients tended to have lower BZDR densities than did non–BZD-treated patients, although the differences did not reach significance. In all MTLE cases, [^{123}I]iomazenil singlephoton emission computed tomography (SPECT) showed decreased BZDR binding in MTL.

Conclusions: In MTLE, BZDR densities decreased parallel to reduction in cell density in most hippocampal subfields, but BZDR density appeared to decrease in excess of neuron loss in CA1. [^{123}I]Iomazenil SPECT might be useful for detecting in vivo changes of BZDR density. **Key Words:** Temporal lobe epilepsy—Hippocampal sclerosis—Benzodiazepine receptor—[^{125}I]iomazenil autoradiography—Neuron loss.

Increasing evidence implicating abnormalities of the excitatory and inhibitory systems in epileptogenesis has been obtained from studies of neurotransmitters and their receptors in the brain. One study has found a decrease of γ-aminobutyric acid (GABA), an inhibitory transmitter, and an increase of glutamic acid, an excitatory transmitter, in epileptogenic foci in patients with temporal lobe epilepsy, which suggests that an imbalance between the two neurotransmitter systems contributes to epileptogenesis (1). The receptors for these excitatory and inhibitory transmitters also have been actively investigated. Abnormalities of the GABA-inhibitory system have been evaluated by measuring quantitative changes of GABA receptors, such as the central benzodiazepine receptor (BZDR) that involves a $GABA_A$ receptor and a conjugated complex including a chloride ion channel. Lower densities of $GABA_A$ receptors and BZDR have been demonstrated in regions closely related to the epileptogenic foci in animal experiments and autopsied brain specimens (2). Some success has been attained in attempts to apply these findings to clinical diagnostic imaging, such as using flumazenil (an antagonist to BZDR) in positron emission tomography (PET) and iomazenil (a partial agonist of BZDR) in single-photon emission computed tomography (SPECT) (3). However, only a limited number of reports have addressed the changes in BZDR at histologic level in surgical specimens from epileptic patients (4–6). In particular, little information is available regarding the use of iomazenil that has recently been introduced into clinical practice.

In this study, we measured BZDR densities in surgical specimens resected from 73 temporal lobe epilepsy patients by using in vitro autoradiography with [^{125}I]ioma-

Accepted April 6, 2002.
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zenil to evaluate changes in the inhibitory system related to epileptogenesis.

SUBJECTS AND METHODS

Patients

Surgical specimens were obtained from 66 temporal lobe epilepsy patients who received no BZDs within 1 month before operation (non-BZD treated) and seven temporal lobe epilepsy patients who had continued to receive BZDs until the time of operation (BZD treated).

The demographic characteristics and clinical features of the 73 patients are shown in Table 1. All were intractable cases with drug-resistant complex partial seizures at least once a month. Before operation, all patients underwent extracranial electroencephalography (EEG) including sphenoid-lead studies during interictal and ictal periods; diagnostic imaging by computed tomography (CT), magnetic resonance imaging (MRI), and regional cerebral blood flow assessment with SPECT; and neuropsychologic tests including the Wada test. Furthermore, [^{123}I]iomazenil SPECT was performed in 10 patients. The findings were assessed together to estimate the extent and location of epileptogenic foci. Long-term EEG monitoring using combined implantation of subdural and depth electrodes (7) also was performed in 23 patients. Based on these examinations, 51 non–BZD-treated patients were diagnosed as having mesial temporal lobe epilepsy (MTLE), in which seizures originated in the mesial structures of one temporal lobe, mainly the hippocampus. For the remaining 15 cases, the diagnosis was non-MTLE, with seizures of extrahippocampal origin.

In the non–BZD-treated patients, the age at onset of seizures ranged from 0 to 23 (mean, 8.3) years in MTLE cases and 0 to 27 (12.0) years in non-MTLE cases. The age at operation ranged from 14 to 46 (25.4) years and 3 to 49 (24.3) years in MTLE and non-MTLE cases, respectively; and the interval from seizure onset to operation from 3 to 34 (16.9) years and 3 to 30 (12.2) years. Subsequently, the epileptogenic foci were excised by anterior temporal lobectomy in 55 patients (MTLE, 40; non-MTLE, 15), and selective amygdalohippocampectomy in 11 patients with MTLE. Histopathologic diagnoses established from the resected specimens were mesial temporal sclerosis in all 51 cases clinically diagnosed as having MTLE; and dysembryoplastic neuroepithelial tumor (five cases), cavernous angioma (three cases), cortical dysplasia (one case), and no abnormalities (six cases) in 15 cases of non-MTLE.

All seven patients who received BZDs had MTLE with hippocampal sclerosis. The age at onset of seizures was 2 to 18 (mean, 7.4) years, the age at operation was 10 to 39 (24.7) years, and the interval from seizure onset to operation was 4 to 37 (17.3) years. The BZDs administered were clonazepam (CZP) in four patients, clorazepate (CLZ) in two, and clobazam (CLB) in one. BZDs were administered for 147 to 6,265 days before operation (mean, 1,353 days).

Before initiation of this study, informed consent was obtained from all the patients for preoperative examinations, surgery, and examination of resected specimens.

[^{125}I]Iomazenil autoradiography

Resected specimens were sliced coronally into tissue blocks 5 mm in thickness. The cross section of the block was oriented perpendicular to the long axis of the hippocampus and represented an area 10 to 15 mm posterior to the anterior pole of the hippocampus. The blocks were frozen to –80°C, and frozen sections 16 μm in thickness were cut and incubated in the receptor-binding buffer for 1 h at 37°C (8,9). The plain buffer was phosphate buffer containing 150 m*M* NaCl. The binding buffer was plain buffer to which 0.2 n*M* [^{125}I]iomazenil (Nihon Medi-physics, Japan) was added for measuring total binding, or 0.2 n*M* [^{125}I]iomazenil plus 1 μ*M* diazepam (DZP) for determining nonspecific binding. After incubation in plain buffer at 0°C for 10 min, the sections were incubated in the binding buffer at 37°C for 60 min. The sections were then washed in cold plain buffer twice and in cold water once. After drying with an air pump, the sections were exposed to Hyperfilm-^{3}H films (Amersham Pharmacia Biotech, Japan). The film was evaluated visually for BZDR distribution and quantitatively analyzed for BZDR density by using an analytic ^{125}I-micro-

TABLE 1. *Clinical characteristics of 73 patients with temporal lobe epilepsy*

	No administration of benzodiazepines		Administration of benzodiazepines
Epileptogenic focus	MTLE	non-MTLE	MTLE
No. of patients (male/female)	51 (28:23)	15 (9:6)	7 (6:1)
Age at seizure onset/mean (yr)	0–23/8.3	0–27/12.0	2–18/7.4
Age at operation/mean (yr)	14–46/25.4	3–49/24.3	10–39/24.7
Interval between onset and operation/mean (yr)	3–34/16.9	3–30/12.2	4–37/17.3
Long-term intracranial recording (cases)	15	5	3
Operation (lobectomy/A-Hectomy; cases)	51 (40:11)	15 (15:0)	7 (5:2)
Pathology (cases)	MTS, 51	DNET, 5; ANG, 3; CD, 1; no abnormality, 6	MTS, 7

MTLE, mesial temporal lobe epilepsy; A-Hectomy, amygdalohippocampectomy; MTS, mesial temporal lobe sclerosis; DNET, dysembryoplastic neuroepithelial tumor; ANG, cavernous angioma; CD, cortical dysplasia.

scale (Amersham Pharmacia Biotech, Japan), a TVIP-4100II TV image processor, and Image Command 4189 (Olympus, Japan). Specific binding was calculated by subtracting the measurement of nonspecific binding from that of total binding.

We selected regions free from damage by the electrodes or operation. To obtain reference data for delineating the regions of interest (ROIs), anatomic mapping was determined based on iomazenil autoradiographic images of adjacent serial sections stained by cresyl violet. The regions measured were cornu ammonis (CA) 4, CA3, CA2, and CA1 of the hippocampus, the pyramidal cell layer of the subiculum, and the molecular and granule cell layers of the dentate gyrus (mDG) according to Lorente de Nó's anatomic system (10). For the parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus, measurements were performed in layers slightly deeper than the cortical surface (layers II, III, and IV; Fig. 1). Layers II to IV that were distinct and easy to measure were selected for BZDR measurement, and the superficial layer I was excluded for the risk of being affected by operative artifacts. In non-MTLE cases, BZDR densities were measured in the sections without pathologic findings. Multiple ROIs (0.3 × 0.3 mm^2, one to 10 squares) were delineated in each region of measurement, and BZDR densities in the ROIs were averaged to obtain the mean BZDR density for the region.

Cell density in hippocampal specimens

The average cell density per unit volume for each hippocampal region was determined by using a cresyl violet–stained serial section adjacent to that for autoradiography, according to Dam (11). The number of pyramidal and granule cell nuclei in a 0.5-mm square was counted and converted to cell count per unit volume (1 mm^3) by using Abercrombie's estimation (12). Cell density was measured for the same ROIs used in BZDR measurement, and a mean value was calculated for each region.

[^{123}I]Iomazenil SPECT

[^{123}I]iomazenil (Nihon Mediphysics, Japan) at 167 to 222 MBq was injected interictally, and a 30-min image acquisition was started 5 min after injection as the early image considered to reflect the cerebral blood flow and at 165 min after injection as the late image reflecting the distribution of BZDR (13,14). With a ring-shaped SPECT head device (HEADTOME-Duo SET070,

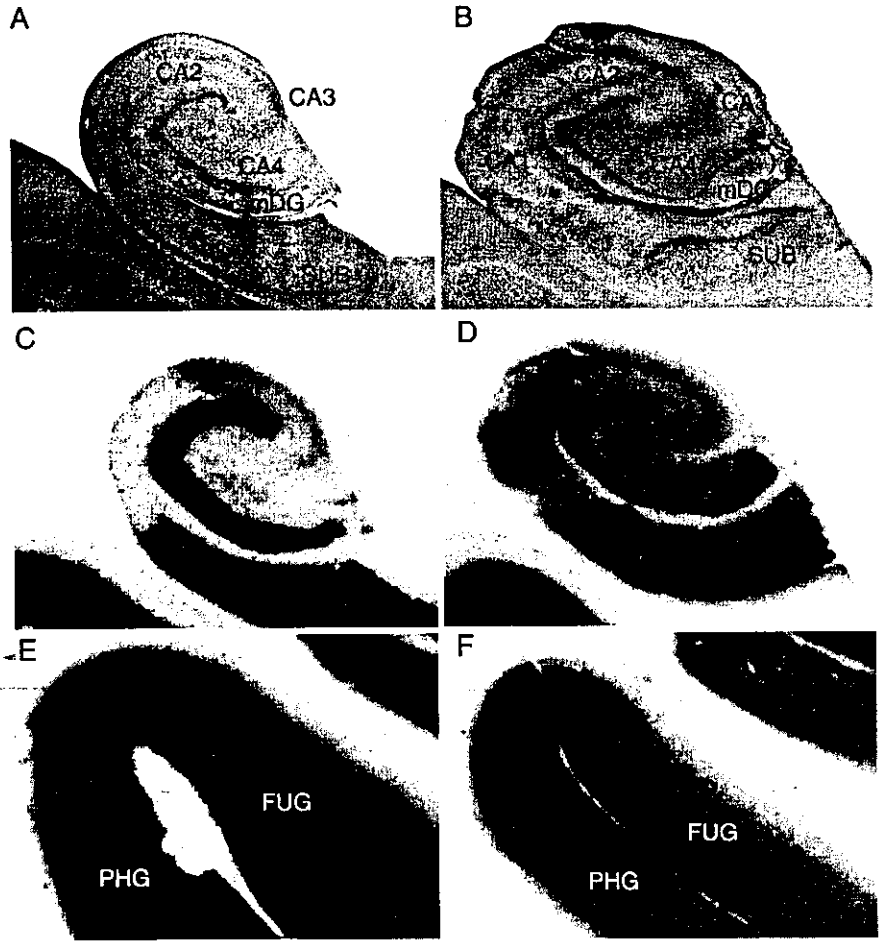

FIG. 1. Autoradiographic patterns and neuron densities of surgically resected specimens from patients with mesial temporal lobe epilepsy (MTLE; **A, C,** and **E**) and non-MTLE (**B, D,** and **F**) receiving no benzodiazepines (BZDs). **A, B:** Cresyl violet–stained sections showing neuron density. **C–F:** [^{125}I]Iomazenil autoradiograms showing distribution of BZD receptor (BZDR). CA, cornu ammonis; mDG, molecular and granule cell layers of the dentate gyrus; SUB, subiculum; PHG, parahippocampal gyrus; FUG, fusiform gyrus. The MTLE cases show decreased accumulation of BZDR binding **(C)** corresponding to the severity of neuron loss **(A)**, especially in the radial and pyramidal layers of CA1, CA3, and CA4. The non-MTLE case shows high accumulation of BZDR **(D)** in the laminated structures of the hippocampus, especially in the mDG and the molecular, radial, and pyramidal cell layers of CA. The BZDR densities in the lateral cortical regions of the temporal lobe did not differ visually between the MTLE and non-MTLE groups **(E, F)**.

Shimazu, Japan), axial, coronal, and sagittal images were obtained at slice intervals of 4.72 mm.

Data analysis

The differences in BZDR density or cell density between the MTLE and non-MTLE groups, and between BZD-treated and non–BZD-treated cases were analyzed with the Mann–Whitney *U* test. Because a normal distribution might not be found in all regions, we used the Mann–Whitney *U* test to analyze all the regions. The correlation between BZDR densities of the hippocampus and lateral cortex for each region was evaluated by using Spearman's correlation coefficient by rank. The BZDR density/cell density ratios were evaluated by using the Mann–Whitney *U* test, because of a lack of normal distribution. The correlation between BZDR density and cell density was evaluated by using Pearson's correlation coefficients in the presence of normal distribution and Spearman's correlation coefficient by rank in the absence of normal distribution.

RESULTS

Visual evaluation of BZDR distribution in non–BZD-treated MTLE and non-MTLE cases

In the MTLE group in which hippocampal sclerosis was evident, a remarkable reduction in BZDR was observed in CA1, CA3, and CA4, and CA2 was relatively spared (Fig. 1A and C). In addition, specific iomazenil binding was greater in the subiculum than in the CA. A wide band of high iomazenil accumulation also was observed from the granule cell layer to the molecular layer of the dentate gyrus. In the non-MTLE group showing no hippocampal sclerosis, BZDR density was homogeneous throughout the hippocampus, retaining the original layered structure (Fig. 1B and D). BZDR density was particularly high in the mDG and the molecular and pyramidal cell layers of the hippocampal gyrus.

The BZDR densities in the lateral cortical regions of the temporal lobe did not differ visually between the MTLE and non-MTLE groups. Bands of high iomazenil binding were observed in layer IV, with a tendency to decrease in the surface (I–III) and deep layers (V,VI), and no accumulation was observed in the white matter (Fig. 1E and F).

Comparison of measured BZDR densities between MTLE and non-MTLE cases of non–BZD-treated cases

Measured BZDR densities (fmol/mg tissue) in various regions for the MTLE and non-MTLE groups receiving no BZD treatment are shown in Table 2. In the MTLE group, BZDR density was lowest in CA1 (mean ± SEM, 4.21 ± 0.47), followed by CA3 (8.19 ± 0.69), CA4 (11.50 ± 1.15), CA2 (15.93 ± 1.02), and mDG (49.53 ± 3.86). BZDR densities in the subiculum, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus (layers II–IV) ranged from 71 to 95. In the non-MTLE group, BZDR densities ranged from 30 to 50 in CA2, CA3, and CA4, and from 80 to 100 in CA1, mDG, subiculum, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus. As seen in Fig. 2, BZDR densities in CA1, CA2, CA3, CA4, and mDG in the MTLE group were significantly lower than the corresponding densities in the non-MTLE group ($p < 0.001$ for CA1, CA3, and CA4; $p < 0.01$ for CA2 and mDG). No significant differences in BZDR density were found between the MTLE and non-MTLE groups in the subiculum, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus.

Correlation of BZDR densities between regions in non–BZD-treated cases

In the hippocampal regions of the MTLE group, a significant and strong correlation in BZDR density was observed between CA1 and CA3 ($n = 37$; $p < 0.0001$; $r = 0.723$), CA2 and CA4 ($n = 35$; $p < 0.0001$; $r = 0.623$), as shown in Table 3. For lateral cortical regions,

TABLE 2. *Regional distribution of benzodiazepine receptor–binding density: MTLE vs. non-MTLE, benzodiazepine-treated vs. non–benzodiazepine-treated cases*

	No benzodiazepines administration		Benzodiazepines administration
	MTLE fmol/mg tissue ± SEM (n)	non-MTLE fmol/mg tissue ± SEM (n)	MTLE fmol/mg tissue ± SEM (n)
mDG	49.53 ± 3.86 (47)	80.54 ± 8.48 (14)	30.75 ± 6.32 (6)
CA4	11.50 ± 1.15 (48)	45.76 ± 4.50 (13)	8.73 ± 2.85 (7)
CA3	8.19 ± 0.69 (38)	37.19 ± 1.85 (11)	9.36 ± 3.94 (6)
CA2	15.93 ± 1.02 (35)	30.11 ± 2.63 (5)	13.31 ± 2.42 (6)
CA1	4.21 ± 0.47 (47)	80.28 ± 7.31 (15)	3.16 ± 0.68 (7)
SUB	70.70 ± 2.87 (50)	81.35 ± 6.06 (15)	63.97 ± 7.15 (7)
PHG	79.77 ± 4.24 (41)	94.53 ± 10.14 (14)	65.74 ± 5.82 (5)
FUG	81.14 ± 4.21 (36)	89.45 ± 7.02 (12)	68.04 ± 3.19 (3)
ITG	94.67 ± 6.47 (18)	102.33 ± 7.88 (9)	74.82 ± 5.74 (2)

MTLE, mesial temporal lobe epilepsy; mDG, molecular and granule cell layers of the dentate gyrus; CA, cornu ammonis; SUB, subiculum; PHG, parahippocampal gyrus; FUG, fusiform gyrus; ITG, inferior temporal gyrus.

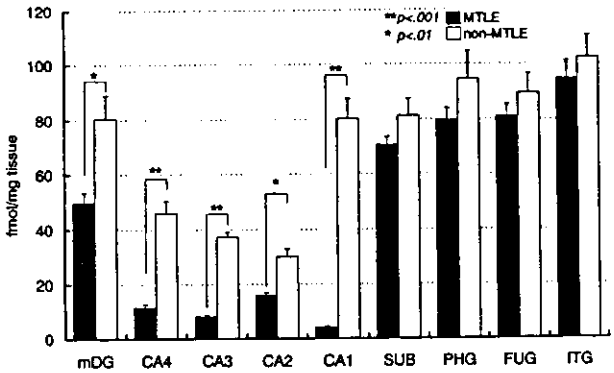

FIG. 2. Comparison of benzodiazepine (BZD) receptor (BZDR) binding densities in mesial temporal lobe epilepsy (MTLE) and non-MTLE groups receiving no BZDs.CA, cornu ammonis; mDG, molecular and granule cell layers of the dentate gyrus; SUB, subiculum; PHG, parahippocampal gyrus; FUG, fusiform gyrus; ITG, inferior temporal gyrus. BZDR densities in CA1, CA2, CA3, CA4, and mDG in the MTLE group are significantly lower than the corresponding densities in the non-MTLE group.

significant correlation was observed among subiculum, parahippocampal gyrus, fusiform gyrus, and inferior temporal gyrus, except between subiculum and inferior temporal gyrus (Table 3). Strong correlations in BZDR density were observed between mDG in the hippocampal region and parahippocampal gyrus ($n = 38$; $p < 0.0001$; $r = 0.702$) as well as fusiform gyrus ($n = 33$; $p < 0.0001$; $r = 0.620$) in the lateral cortical region. No significant correlation in BZDR density was observed between all the regions in non-MTLE cases.

Comparison of hippocampal BZDR density and cell density between non–BZD-treated MTLE and non-MTLE cases

Measured cell densities ($\times 10^3$ neuron/mm^3) in various hippocampal regions for the MTLE and non-MTLE groups receiving no BZD treatment are shown in Table 4. In the MTLE group, cell densities in all hippocampal regions were lower than those in non-MTLE. Cell density of hippocampus was lowest in CA1, followed by CA4, CA3, CA2, and mDG. Conversely, in non-MTLE group, cell density was lowest in CA4, followed by CA2, CA3, CA1, and mDG. The cell densities in all the hippocampal regions were significantly lower in the MTLE group compared with the non-MTLE group (mDG, CA4, CA3, and CA1, $p < 0.0001$; CA2, $p < 0.01$), and was most marked in CA1 followed by CA4, CA3, and CA2.

Next, to compare the degrees of reduction in BZDR density and neuron loss, we calculated the BZDR density/cell-density ratios in the hippocampal regions and compared them between the MTLE and non-MTLE cases (Fig. 3). In CA1, the BZDR/cell ratio was significantly lower in MTLE cases (0.0072) than in non-MTLE cases (0.0115; $p < 0.001$). No significant differences were observed in the other regions.

Correlation between hippocampal BZDR density and cell density in non–BZD-treated cases

Of the 66 specimens examined, both BZDR density and cell density could be measured in CA1 in 56 cases, in CA2 in 38 cases, in CA3 in 47 cases, in CA4 in 55 cases, in mDG in 37 cases, and in parahippocampal gy-

TABLE 3. *Correlation of benzodiazepine receptor density between regions in MTLE and non-MTLE*

	mDG	CA4	CA3	CA2	CA1	SUB	PHG	FUG	ITG
MTLE									
mDG	—	n.s.	n.s.	n.s.	n.s.	0.502 (47)[b]	0.702 (38)[a]	0.620 (33)[a]	n.s.
CA4		—	n.s.	0.623 (35)[a]	n.s.	n.s.	n.s.	n.s.	n.s.
CA3			—	0.552 (32)[b]	0.723 (37)[a]	n.s.	n.s.	n.s.	n.s.
CA2				—	0.549 (34)[b]	n.s.	n.s.	n.s.	n.s.
CA1					—	n.s.	n.s.	n.s.	n.s.
SUB						—	0.800 (41)[a]	0.746 (36)[a]	n.s.
PHG							—	0.795 (35)[a]	0.827 (17)[a]
FUG								—	0.773 (18)[a]
ITG									—
Non-MTLE									
mDG	—	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CA4		—	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CA3			—	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
CA2				—	n.s.	n.s.	n.s.	n.s.	n.s.
CA1					—	n.s.	n.s.	n.s.	n.s.
SUB						—	n.s.	n.s.	n.s.
PHG							—	n.s.	n.s.
FUG								–	n.s.
ITG									—

Results expressed as r values (number of cases).

MTLE, mesial temporal lobe epilepsy; mDG, molecular and granule cell layers of the dentate gyrus; CA, cornu ammonis; SUB, subiculum; PHG, parahippocampal gyrus; FUG, fusiform gyrus; ITG, inferior temporal gyrus; n.s., not significant.

[a] $p < 0.0001$.

[b] $p < 0.001$.

TABLE 4. *Regional distribution of cell density in non-benzodiazepine-treated cases*

	MTLE $\times 10^3$ neurons/mm^3 ± SEM (n)	non-MTLE $\times 10^3$ neurons/mm^3 ± SEM (n)
mDG	166.40 ± 9.53 (27)	307.09 ± 17.03 (10)
CA4	8.61 ± 0.77 (44)	43.68 ± 3.67 (13)
CA3	19.80 ± 2.25 (39)	64.61 ± 4.59 (11)
CA2	31.02 ± 2.03 (35)	56.63 ± 3.79 (4)
CA1	4.57 ± 0.81 (43)	67.01 ± 2.67 (13)

MTLE, mesial temporal lobe epilepsy; mDG, molecular and granule cell layers of the dentate gyrus; CA, cornu ammonis.

rus in 11 cases. A significant correlation between BZDR density and cell density was observed in CA1 ($p < 0.0001$; $\rho = 0.848$, Spearman's correlation coefficient by rank), CA3 ($p < 0.0001$; $r = 0.840$; Pearson's correlation coefficients), CA4 ($p < 0.0001$; $r = 0.890$, Pearson's), mDG ($p < 0.0001$; $r = 0.834$, Pearson's), CA2 ($p < 0.001$; $r = 0.521$, Pearson's), and parahippocampal gyrus ($p < 0.05$; $r = 0.645$, Pearson's; Fig. 4).

Comparison of BZDR densities in BZD-treated and non-BZD-treated cases

In the seven BZD-treated cases, all diagnosed as MTLE, the mean BZDR density was lowest in CA1, followed by CA4, CA3, CA2, and mDG (Table 2). BZDR density was on average ~17% lower in BZD-treated cases than in non–BZD-treated cases. Except in CA3, the mean BZDR densities in all regions, especially in mDG (reduction rate, 38%), were lower in BZD-treated than in non–BZD-treated cases, although the differences did not reach statistical significance (Table 2).

Comparison of BZDR densities with [^{123}I]iomazenil SPECT between non–BZD-treated MTLE and non-MTLE cases

[^{123}I]Iomazenil SPECT was performed in seven MTLE patients and three non-MTLE patients. All MTLE patients had mesial temporal sclerosis, and the three non-MTLE patients had no histopathologic abnormality. In all seven MTLE patients, visual evaluation of [^{123}I]iomazenil SPECT late images revealed a reduced accumulation of BZDR binding in the ipsilateral temporal lobe mesial region of epileptogenic focus site, including the hippocampus and partially involving lateral cortical regions, compared with contralateral temporal lobe (Fig.5). However, no such findings were observed in the temporal lobe mesial region in three non-MTLE patients.

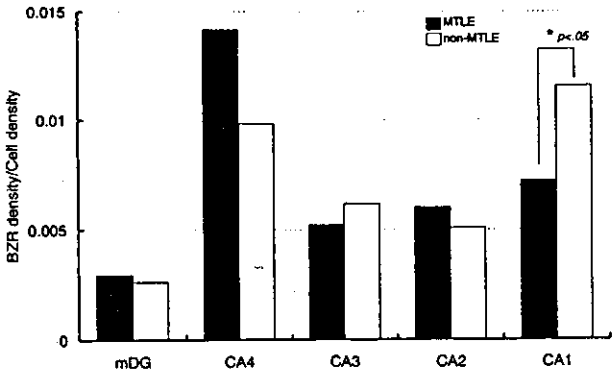

FIG. 3. Comparison of benzodiazepine (BZD) receptor (BZDR) density to cell-density ratios in mesial temporal lobe epilepsy (MTLE) and non-MTLE groups receiving no BZDs. CA, cornu ammonis; mDG, molecular and granule cell layers of the dentate gyrus. In the MTLE group, the BZDR density/cell-density ratio is significantly lower in CA1 compared with the non-MTLE group ($p < 0.05$).

DISCUSSION

In 1979 Ribak et al. (2) reported that GABAergic inhibitory synapses were decreased at epileptogenic foci, and suggested a possible contribution of GABAergic neuronal loss to the formation of epileptogenic foci. Region-specific decreases in binding to the $GABA_A$–BZDR–ionophore complex have been demonstrated by immunostaining of GABA receptors (15), autoradiography of BZDR, and in vivo diagnostic imaging with flumazenil PET (16–18) or iomazenil SPECT (19–21). In particular, autoradiography allows quantitation of receptor densities at histologic level, and BZDR density has been evaluated with autoradiography by using iomazenil (5), flumazenil (4,22), or flunitrazepam (6). In this study, we measured BZDR density with autoradiography by using iomazenil, for which few data are currently available. With this method, we evaluated BZDR densities in 73 surgical specimens of temporal lobe epilepsy, which is the largest series among similar studies. Iomazenil, a partial inverse agonist of BZDR, has been reported to distribute in the brain similar to the BZDR antagonist, flumazenil (23,24). The affinity of iomazenil for BZDR is higher than that of flumazenil and flunitrazepam (9). Hence [^{125}I]iomazenil autoradiography images are superior in sensitivity and anatomic resolution, as demonstrated in previous reports (9,25) and the present study.

A limitation of the present study was the unavailability of normal control specimens. We compared the results of MLTE cases with those of non-MTLE cases. BZDR density in our non-MTLE specimens, which showed no sclerosis, was higher in hippocampal CA1, subiculum, and mDG regions than in CA2, CA3, or CA4. In a study of BZDR distribution in normal human brain after autopsy with autoradiography by using [^{3}H]flunitrazepam, Zezula et al. (26) found BZDR density to be particularly high in the cerebral cortex and hippocampus, especially in temporal cortical layer IV, subiculum, CA1, and mDG. The results obtained in our non-MTLE cases were consistent with those for normal hippocampus reported by Zezula et al. (26), presumably reflecting normal BZDR distribution in non-MTLE cases. In addition, Loup et al. (27) compared the distribution of $GABA_A$-receptor subtypes in human temporal lobe epilepsy in