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Focal ictal direct current shifts in human epilepsy as studied by subdural and scalp recording

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Summary

In order to clarify further the characteristics of ictal direct current (DC) shifts in human epilepsy, we investigated them by subdural and scalp recording in six and three patients, respectively, both having mainly neocortical lobe epilepsy (five with frontal lobe epilepsy, two with parietal lobe epilepsy and two with temporal lobe epilepsy). By using subdural electrodes made of platinum, ictal DC shifts were observed in 85% of all the recorded seizures (89 seizures) among the six patients, and they were localized to just one or two electrodes at which the conventional initial ictal EEG change was also observed. They were closely accompanied by the electrodecremental pattern in all patients except for one in whom 1 Hz rhythmic activity was superimposed on clear negative slow shifts. Seizure control after resection of the cortex, including the area showing DC shifts, was favourable irrespective of histological diagnosis. Scalp-recorded ictal slow shifts were observed in 23% of all the recorded seizures (60 seizures) among the three patients. They were, like the subdurally recorded ones, mainly surface-negative in polarity, closely related to the electrodecremental pattern and consistent in their location. It seems that scalp-recorded DC shifts were detected particularly when seizures were clinically intense, while no slow shifts were observed in small seizures. It is concluded that at least subdurally recorded ictal slow shifts are clinically useful before epilepsy surgery to delineate more specifically an epileptogenic area as well as to further confirm the conventional initial ictal EEG change, and that scalp-recorded ictal slow shifts also have high specificity although their low sensitivity is to be taken into account.

Keywords: ictal DC shift; ictal EEG; subdural recording; scalp recording; epilepsy

Abbreviations: DC = direct current; FLE = frontal lobe epilepsy; HFF = high frequency filter; LFF = low frequency filter; MTLE = mesial temporal lobe epilepsy; NLE = neocortical lobe epilepsy; PLE = parietal lobe epilepsy; SEP = somatosensory evoked potential; TLE = temporal lobe epilepsy

Introduction

Direct current (DC) field potentials, which are recorded by using extremely long or even infinite time constants, directly reflect physiological as well as pathological changes in central neurons and glia (Caspers, 1974; Speckmann and Elger, 1993). In experimental studies, localized negative DC shifts were recorded during penicillin-induced seizures, and they occur in association with sustained paroxysmal activity, suggesting that these negative shifts are an expression of cellular depolarization (Goldring, 1963; Eidelberg and Meyerson, 1964; Ayala *et al*., 1973). The DC shifts were of maximal voltage at the centre of the focus and the paroxysmal activity had a more extensive distribution than the negative DC shift (Gumnit and Takahashi, 1965).

Based on the above findings, we recently demonstrated ictal DC shifts in three patients with neocortical lobe epilepsy (NLE) by using subdural electrodes chronically implanted for the purpose of epilepsy surgery (Ikeda *et al*., 1996). The investigations showed that (i) ictal DC shifts were mainly surface-negative in polarity; (ii) they started

earlier than the conventional ictal EEG onset; (iii) they were seen in a more restricted area compared with the dimension defined by the conventional ictal EEG changes; and (iv) their occurrence often coincided with the electrodecremental pattern. However, since the above findings were derived from a small number of patients, several concerns still remain unsolved. (i) It is unknown whether seizure focus in mesial temporal lobe epilepsy (MTLE) in humans also shows similar slow shifts or not. (ii) In the previous study, since the number of seizures recorded in each patient ranged from 1–4, the sensitivity and specificity of the subdurally recorded ictal DC shifts still remain unknown. (iii) The nature of ictal DC shifts in relation to the histological findings of the epileptogenic area is not completely clarified and further investigation based on a larger number of patients is needed.

Ictal DC shifts were also studied by scalp electrodes. Chatrian *et al*. (1968) reported slow negative shifts accompanied by 3 Hz spike and wave complexes in patients with petit mal, but otherwise, little was reported in humans. It is most likely that the scalp-recorded ictal DC shifts were poorly identified in humans mainly due to movement artefacts during seizures and limited capability of amplifiers used in the past (Cooper *et al*., 1980). Regardless of the kind of metals used for electrodes, a large input impedance, i.e. >50 MΩ, which was not usually available in the past, is essential to record stable slow shifts (Cooper *et al*., 1980). We recently demonstrated scalp-recorded focal ictal DC shifts in a patient with tonic seizures whose initial ictal EEG showed a diffuse electrodecremental pattern (Ikeda *et al*., 1997*a*). However, as in subdural recording of ictal DC shifts, the sensitivity and specificity of the scalp-recorded ictal DC shifts and the characteristics of the slow shifts in relation to the conventional ictal pattern still remain to be clarified. Furthermore, the comparison of ictal DC shifts in subdural and scalp recording could help in understanding their neurophysiological nature and clinical usefulness.

After publishing subdurally recorded ictal DC shifts obtained from three patients (Ikeda *et al*., 1996), we investigated six more consecutive patients with subdural electrodes. Also for the scalp-recorded ictal DC shifts based on a patient with partial seizures (Ikeda *et al*., 1997*a*), they were further investigated in three other patients with extra-temporal lobe epilepsy. Therefore, in the present study, we will further clarify the clinical significance of ictal DC shifts revealed by subdural and scalp recording, with special emphasis placed on their sensitivity and specificity for identifying epileptic events. Some of the results of subdural recording of ictal DC shifts among the present patients were reported in an abstract form (Ikeda *et al*., 1997*b*). Other neurophysiological data from these patients were described elsewhere (Ikeda *et al*., 1999; Mikuni *et al*., 1997; Yazawa *et al*., 1997, 1998).

Patients and methods

Subdural recording

Patients with subdural electrodes (patients 1–6) (Table 1)

Six consecutive patients with medically intractable partial seizures had subdural grid electrodes chronically implanted as a part of their final presurgical evaluation in Kyoto University Hospital (Table 1).

The ages of the patients ranged between 18 and 52 years (mean 31 years) and age of seizure onset ranged from 2–47 years (mean 18 years). Previously all had undergone prolonged non-invasive video/EEG monitoring which included sphenoidal electrode, brain imaging studies, i.e. MRI, ictal and interictal SPECT (single photon emission computed tomography) and FDG-PET ([^{18}F]fluorodeoxy-glucose-PET), psychometric evaluation and intracarotid amobarbital test. Four patients (patients 2–4 and 6) had neocortical lobe epilepsy (NLE); three had frontal lobe epilepsy (FLE) and one parietal lobe epilepsy (PLE). In two other patients (patients 1 and 5), the mesial temporal structure was epileptogenic and was thus diagnosed as temporal lobe epilepsy (TLE). In patient 5, the right mesial temporal structure as well as the right posterior lateral temporal area were judged as epileptogenic. The two patients with TLE had hippocampal atrophy on MRI, and among four patients with NLE, three had local abnormal findings on MRI.

Following the above monitoring, invasive monitoring was performed to define the location of an epileptogenic area. Informed consent was obtained from all the patients after the purpose and possible consequence of the studies were explained according to the Clinical Research Protocol No. 79 approved by the committee of medical ethics, Graduate School of Medicine and Faculty of Medicine, Kyoto University. Consequent to the invasive recording, the six patients underwent surgical resection of the epileptogenic zone.

Invasive ictal EEG recording

In patients 1–6, a long-term video/EEG monitoring was carried out for 7 days in a hospital room, as in the previous study (Ikeda *et al*., 1996). All subdural electrodes were made of platinum (AD-TECH Corp., Racine, USA) and were arranged as grid (8×2, 5×4) or strip (1×4) with centre-to-centre inter-electrode distance of 1 cm. Each electrode used in patients 1–5 had the diameter of 3 mm for recording surface and that used in patient 6 had the diameter of 5 mm.

For recording cortical potentials in patients 1 and 5, all subdural electrodes were referenced to one of the subdural electrodes placed over the lateral convexity, which did not elicit any symptom when stimulated or did not show any ictal or interictal epileptiform discharge. In patients 2–4 and 6, all subdural electrodes were referenced to a scalp

Table 1 *Clinical profile of six patients with medically intractable seizures evaluated by subdural electrodes*

	Patient					
	1	2	3	4	5	6
Age (years)/sex	30/F	23/F	52/M	25/M	38/M	18/M
Age at seizure onset (years)	12	7	47	18	10	2
Diagnosis	Left TLE	Right FLE	Right FLE	Right FLE	Right TLE	Left PLE
Seizure type	CPSz	SPSz*	SPSz* → GTCSz	SPSz	CPSz	CPSz
Seizure frequency	4/month	5/day	2/week	3/day	1/week	1/day
Scalp EEG						
Interictal spikes	Fp1, Sp1	None	Right frontal	None	Right hemiphere	Left frontocentral
Ictal discharges	Left frontal	None	Right vertex	Obscured by EMG	Right temporal	Left parietal → left frontal
MRI	Left HA	T_2-high lesion at right mesial frontal	T_2-high lesion at right frontal	Normal	Right HA	T_2-high lesion at left parietal
Histology	HS	Gliosis	Astrocytoma (gII)	Gliosis	HS and dysplasia	Dysplasia
Subdural electrode placement	Left temporal	Right mesial frontal	Right medial frontal	Right rolandic	Right temporal	Left parietal and mesial frontal
Surgical outcome[†]	Ia	IIa	Ia	IIb	IIa	IIa
Follow-up period (months)	30	14	12	21	23	5

TLE = temporal lobe epilepsy; FLE = frontal lobe epilepsy; PLE = parietal lobe epilepsy; CPSz = complex partial seizures; SPSz = simple partial seizures; GTCSz = generalized tonic-clonic seizures; HA = hippocampal atrophy; HS = hippocampal sclerosis; gII = grade II; *SMA seizure; [†]Engel's classification of seizure control in this and other relevant tables.

electrode placed on the skin over the mastoid process contralateral to the side of the electrode implantation (on the left in patients 2–4 and on the right in patient 6).

All ictal EEGs in patients 2–6 were digitized by an analogue-to-digital converter at a sampling rate of 200 Hz per channel, and stored on an EEG 2100 (Nihon Kohden, Tokyo, Japan) for subsequent review and analysis. In patients 1 and 4, during the initial 2 days of monitoring, EEG signals were recorded on compact magnetic tapes as analogue signal by using a compact video/EEG monitoring system (EL1102, NEC San-ei, Tokyo, Japan). Seizures were recorded with a low frequency filter (LFF) setting (–3 dB of down point) on an AC amplifier of 0.016 Hz in all patients. A high frequency filter (HFF) (–3 dB of down point) was set to 60 Hz. Recording sensitivity was set to 5 mV full-scale (12 bits) for analogue signal monitoring (EL1102) (BIOTOP, NEC San-ei) in patients 1 and 4, and to 50–75 μV/mm for digital signal monitoring (EEG 2100) in patients 2–6.

In patients 2–4 and 6, EMG was recorded from the left tibialis anterior, bilateral tibialis anterior, left orbicularis oculi and right deltoid muscles, respectively, during seizure monitoring. LFF, HFF and sensitivity for the EMG recording were set to 5 Hz, 60 Hz and 50 μV/mm, respectively. A 60 Hz notch filter was applied to all channels.

All the patients had further examinations for cortical mapping including cortical electric stimulation and recording of somatosensory evoked potentials (SEPs) (Luders *et al*., 1987), and the final decision for cortical resection was made by taking into account both the functional and seizure mappings.

Table 2 *Clinical profile of three patients with NLE evaluated by scalp electrodes*

	Patient		
	7	8	9
Age (years)/sex	19/F	10/F	31/F
Age at seizure onset (years)	14	9	15
Diagnosis	Right FLE	Right PLE	Left FLE
Seizure type	SPSz*	SPSz	SPSz*
Seizure frequency	10/day	50/day	10/day
Scalp EEG			
Interictal spikes	C4, Cz	Pz, Cz	Cz
Ictal discharges	C4, Cz	Cz	Cz
MRI	Normal	T_2-high lesion at right parietal	T_2-high lesion at left mesial frontal

*SMA seizure.

Scalp recording

Patients with scalp electrodes (patients 7–9) (Table 2)

We studied three patients with intractable partial seizures who met the following criteria: (i) diagnosis of partial epilepsy other than MTLE, and (ii) frequent seizures (at least 10 per day) which enabled us to evaluate the sensitivity of the occurrence of slow ictal shifts more accurately.

The age of the patients ranged between 10 and 31 years (mean 19 years), and the age of seizure onset ranged from 9–15 years (mean of 11 years) (Table 2). All three patients had NLE; two had FLE and one had PLE. Two patients (patients 7 and 8) with FLE had supplementary motor area

(SMA) seizures, which was clinically documented by video/EEG monitoring. Two patients (patients 8 and 9) had focal abnormal lesion on MRI.

Non-invasive ictal EEG recording

For patients 7–9, long-term video/EEG monitoring was carried out for 2–4 days in a hospital room, as reported previously (Ikeda *et al*., 1997*a*). Scalp EEGs were recorded by a portable, digital electroencephalograph (EEG 2100) with shallow cup electrodes made of silver/silver chloride (ON95–029, Unique Medical Corp., Tokyo, Japan), which were 11 mm in diameter and attached on the scalp with collodion according to the International 10–20 System. For data acquisition, LFF was set to 0.016 Hz and HFF to 30 or 60 Hz, depending on the sampling rate of 100 or 200 Hz, respectively, as described below. A 60 Hz notch filter was applied to all channels. All signals were digitized by an analogue-to-digital converter at a sampling rate of 200 Hz per channel for the initial EEG evaluation and at 100 Hz for subsequent long-term seizure recording. All data were stored on magneto-optical disks for subsequent review and analysis. The EMG was recorded from the right deltoid muscle for patient 7, left tibialis anterior and gastrocnemius muscles for patient 8, and the right deltoid muscle for patient 9 during the monitoring. LFF, HFF and sensitivity for the EMG recording were set as described for patients 2–4 and 6 (see above).

Analysis and interpretation of EEG findings

Seizures not associated with habitual clinical semiology were excluded from the analysis.

In patient 5, no habitual seizures occurred during the monitoring over a total period of 6 days, while only subclinical seizure pattern was recorded. However, those data were adopted for analysis because sufficient seizure control was achieved after resection of the area defined by the subclinical seizures.

Clinical onset was determined by the monitored EMG onset which reflected well the clinical behaviours in patients 2–4, 6 and 7–9. For patient 5, the habitual clinical seizures were not recorded as described above, and for patient 1 the clinical onset time could not be determined precisely because the habitual seizures started with psychic aura which was initially associated with only subtle behaviour changes. When displaying and analysing the recorded seizures, an LFF of 1.0 Hz was applied to evaluate the conventional ictal EEG finding, and that of 0.016–0.03 Hz was applied to evaluate the ictal DC shifts. In scalp-recorded EEG, slow potentials were displayed by using the averaged reference. In patient 1, all seizures were recorded as analogue signal with an LFF of 0.016 Hz.

In the present study, an ictal DC shift was defined as slow potential which was not detected by LFF of 1.0 Hz, but only detected by opened LFF as described above, and in which upward or downward phase of each slow shift lasted at least 3 s. It could be either negative or positive in polarity in the initial phase of waveform. In subdural recording, peak to peak amplitude along the entire waveform could be at least 200 μV, preferably >1 mV, and in scalp recording, the amplitude could be at least 50 μV, preferably >100 μV. The simultaneous occurrence of repetitive discharges from several to 30 Hz of frequency were not essential for the definition of ictal DC shift. Those definitions, especially in the subdural recording, were based on the authors' previous findings (Ikeda *et al*., 1996, 1997*a*). For all the ictal EEG findings in each patient, the agreement by two board-certified EEGers (A.I. and H.S.) was regarded as the final judgement. Incidence rate of ictal DC shift was obtained for each individual patient as the number of seizures which showed ictal DC shifts divided by the number of all the recorded seizures. In the present and previous papers (Ikeda *et al*., 1996, 1997*a*), we adopted the term 'ictal DC shifts', but we recognize that ictal slow shifts in our studies do not purely represent a 'true' DC shift in the strict sense, because we used AC amplifier with a long time constant.

Results

Subdural recording (Table 3)

Conventional ictal EEG change

Among the six patients evaluated by subdural recording, 8–34 seizures (average 17.5) were recorded per patient. The initial ictal EEG changes consisted of low to middle amplitude, fast activity in three patients (patients 1, 4 and 5). In one patient (patient 2), the initial ictal EEG change was disappearance of the background activity while fast and low amplitude activity was hardly visible. In two patients (patients 3 and 6), the initial EEG change was rhythmic slow (1–2 Hz) activity.

Among four patients (excluding patients 1 and 5), the onset time of the initial ictal EEG changes preceded the clinical onset as determined by the EMG activity in three patients, and in the remaining patient the two events coincided. Therefore, it was judged that the EEG changes observed in those patients represent the activity arising from the ictal onset zone or just nearby. In patient 1, the time interval between the clinical onset and the initial EEG changes was not clearly determined (see Patients and methods), but the 15 Hz fast activity seen in this patient was regarded as the initial ictal changes arising from the ictal onset zone. In patient 6, the 20 Hz fast activity was regarded likewise.

Ictal DC shifts

Among 105 seizures recorded from the six patients, 89 seizures (85%) showed clear ictal slow potentials and they were localized to one or two particular electrodes for each patient (Table 3). Incidence rate of ictal DC shifts varied between 42 and 100% among six patients, and in two patients

Table 3 *Ictal EEG findings in six patients with intractable seizures evaluated by subdural electrodes*

	Patient					
	1	2	3	4	5	6
No. of recorded seizures*	8	34	13	12	26	12
Clinical onset†	(Psychic aura)	Left foot tonic contraction	Left foot tonic contraction	Bilateral eyelids tonic contraction	(Somatosensory aura)	Right foot tonic contraction
Initial ictal EEG discharge‡	15 Hz middle amplitude activity	Diffuse attenuation	1 Hz rhytnmic activity	20 Hz low amplitude activity	20 Hz middle amplitude activity	2 Hz rhythmic activity
Focal ictal EEG discharge‡	As above	2 Hz rhythmic activity	As above	As above	As above	As above
Time to clinical onset	ND	0 s	–10 to –5 s	–3 to –1.5 s	ND	–20 to –10 s
Ictal DC shifts						
Number of seizures§	8	34	10	5	21	11
Polarity	Negative	Negative	Negative	Negative and positive	Negative	Negative
Number of electrodes	1	2	1	2	1	1
Time to clinical onset	–	0 s	–13 to –5 s	–2 s	–	+5 to +20 s
Time to ictal EEG discharges	No difference	–4 s	–3 to 0 s	No difference	No difference	+25 to +30 s
Incidence rate¶	100%	100%	76%	42%	81%	92%

ND = not determined. *Only seizures showing habitual clinical semiology were accepted. †Determined by the monitored EMG onset in patients 2–4 and 6 as described in the Patients and methods. In patient 1, clear clinical onset was not precisely determined because of only slight behaviour (psychic aura) changes, and the habitual clinical seizures were not recorded in patient 5. ‡Judged by the EEG displayed with LFF of 1.0 Hz as described in the Patients and methods section. §Judged by the EEG displayed with LFF of 0.016 Hz as described in the Patients and methods section. ¶Calculated by the number of seizures with clear ictal DC shifts in §divided by the total number of recorded seizures in *.

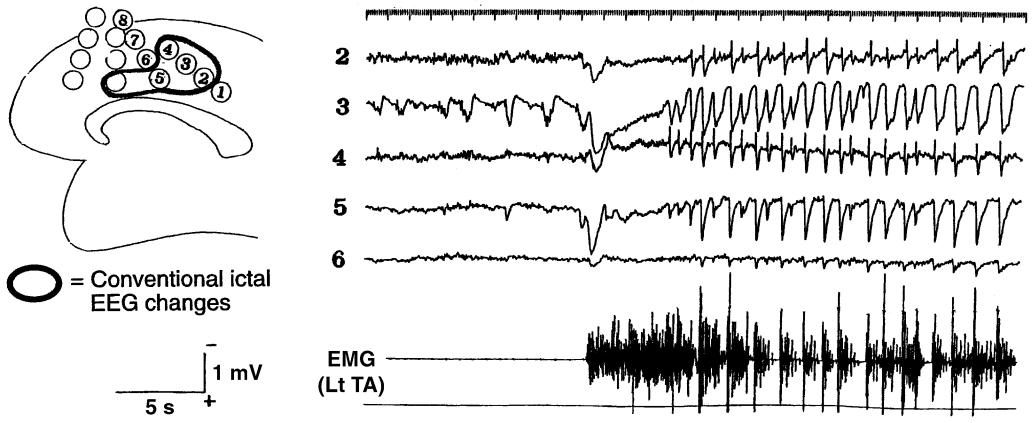

Fig. 1 Subdurally recorded ictal DC shifts associated with a simple partial seizure in patient 2 with right frontal lobe epilepsy. Just after a large transient positive activity at the time of clinical seizure onset as demonstrated by tonic EMG discharges from the left tibialis anterior muscle (Lt TA), negative shifts are localized exclusively at electrodes 3 and 5. The activity is within the area showing the conventional ictal EEG changes indicated by a large closed circle. EEG is displayed with LFF setting of 0.016 Hz.

(patients 1 and 2) all the recorded seizures contained clear ictal DC shifts.

Negative slow shifts were mainly seen in five patients (Figs 1, 2, 4 and 5), and negative and positive slow shifts were simultaneously observed in one patient (Fig. 3). With regard to the time interval between the DC shift onset and the clinical onset in four patients (excluding patient 1 and 5), in two patients the onset of the ictal DC shifts preceded the clinical onset by 2–13 s (Figs 2 and 3), and one patient (patient 2) showed the simultaneous onset of ictal DC shifts and clinical behaviours (Fig. 1). In another patient (patient 6), the ictal DC shifts were observed 5–20 s after the clinical onset (right foot tonic contraction) when 2 Hz rhythmic activity was replaced by low amplitude fast activity (as

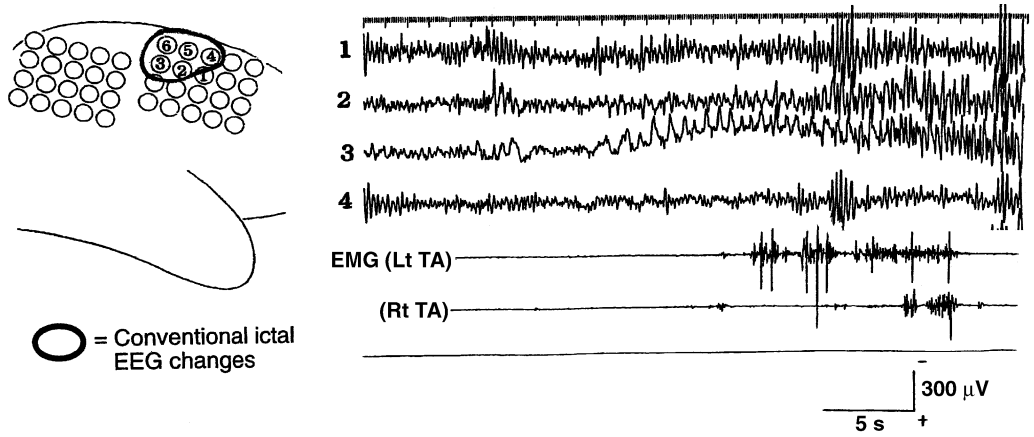

Fig. 2 Subdurally recorded ictal DC shifts associated with a simple partial seizure in patient 3 with right frontal lobe epilepsy. At 5–10 s before the clinical onset [determined by EMG activity of the left tibialis anterior muscle (Lt TA)], negative slow shift is localized exclusively at electrode 3 when 1 Hz rhythmic activity starts occurring. EEG is displayed with LFF setting of 0.016 Hz.

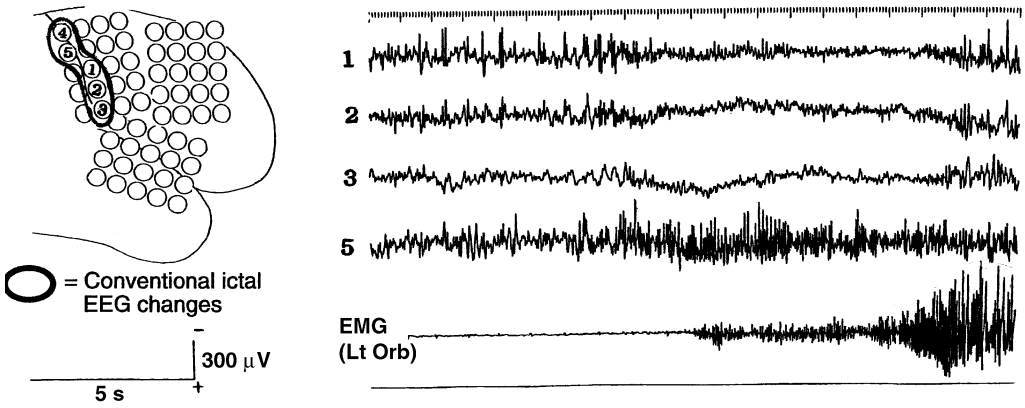

Fig. 3 Subdurally recorded ictal DC shifts associated with a simple partial seizure in patient 4 with right frontal lobe epilepsy. At 1.5–3 s before the clinical onset as determined by EMG activity of the left orbicularis oculi muscle (Lt Orb), negative and positive shifts are seen at electrodes 2 and 3, respectively, when 20 Hz low amplitude activity begins. EEG is displayed with LFF setting of 0.05 Hz.

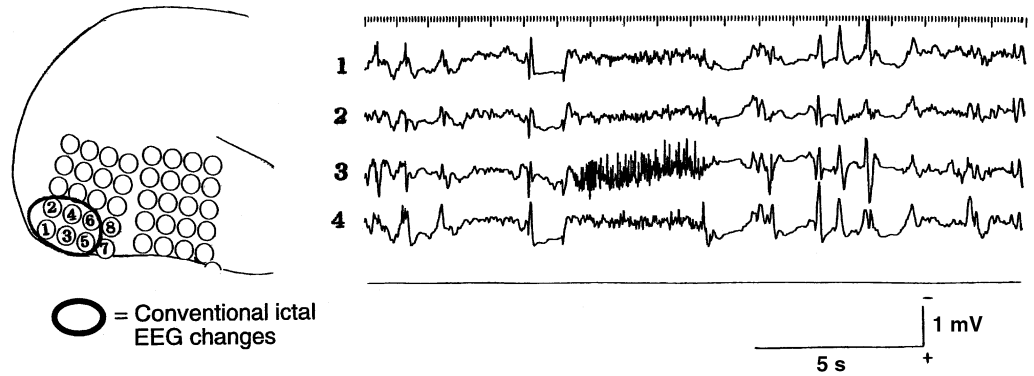

Fig. 4 Subdurally recorded, subclinical, ictal DC shifts in patient 5 with right temporal lobe epilepsy. Negative slow shift is seen at electrode 3, where 20 Hz middle amplitude activity is seen simultaneously. EEG is displayed with LFF setting of 0.05 Hz.

shown by a large arrow in Fig. 5). In all the six patients, the slow shifts were localized in a more restricted area than the conventional ictal EEG finding.

When comparing the onset time between the ictal DC shifts and the conventional ictal EEG change, two patients (patient 2 and 3) had the earlier onset of ictal DC shifts, and three patients (patients 1, 4 and 5) had simultaneous onset. Only in one patient (patient 6), the ictal DC shifts followed

the conventional ictal EEG changes, but the former nearly coincided with the onset of low amplitude fast activity (Fig. 5). In this patient, the initial ictal EEG change consisted of 2 Hz rhythmic activity and the electrodecremental pattern occurred after the clinical onset.

With regard to the relationship between the ictal DC shifts and the electrodecremental pattern, in five patients the slow shifts started just when the electrodecremental pattern (low to middle amplitude and fast activity in four patients and diffuse attenuation in one patient) appeared. In one patient (patient 3) the slow shifts started when 1 Hz rhythmic activity appeared.

Scalp recording (Table 4)

Conventional ictal EEG change

In three patients (7–9), 10–28 seizures (20 on average) were recorded in each. In all the recorded seizures in patients 7 and 8, and in 53% of the seizures in patient 9, initial ictal EEG changes were observed. In patients 7 and 9 both of whom had clinical SMA seizures, low amplitude, 15–20 Hz fast activity was observed at the vertex area 1–3 s before the clinical onset as determined by the EMG onset. Patient 8 had focal motor seizures in the left foot. Repetitive positive spikes at Cz were seen at -5 to +5 s with respect to the clinical onset as determined by the EMG activity from the left tibialis anterior or gastrocnemius muscles. During clinical seizures, clonic EMG discharges were observed initially and they were followed by tonic and then clonic discharges. At times seizures started with tonic EMG discharges. During the clonic phase in all seizures positive spikes always preceded the EMG discharges by 25–30 ms.

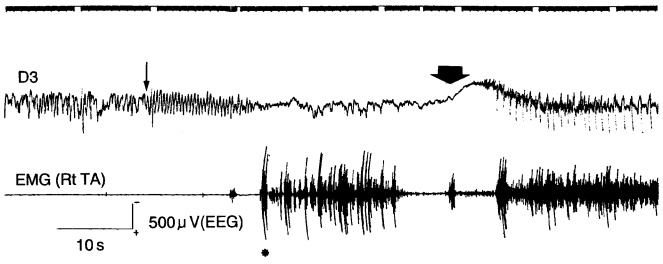

Fig. 5 Subdurally recorded ictal DC shifts associated with a complex partial seizure in patient 6 with left parietal lobe epilepsy. At 25–35 s after the initial ictal EEG onset, i.e. 2 Hz rhythmic activity (as indicated by a small arrow), a slow negative shift is observed at electrode D3 (as indicated by a large arrow) when an electrodecremental pattern is seen. Seizure onset is indicated by an asterisk on the EMG. EEG is displayed with LFF setting of 0.016 Hz.

Ictal DC shifts

When the EEG was displayed with an LFF of 0.016 Hz, slow potentials were superimposed on the initial ictal EEG discharges in all three patients.

Out of 60 recorded seizures from the three patients, 14 seizures (23%) showed clear ictal slow potentials (Table 4). Incidence rate of ictal DC shifts was 40% in patient 7, 25% in patient 8 and 14% in patient 9.

In patient 7, slow negative shifts started occurring exclusively when the middle amplitude, 15 Hz fast activity was observed (Fig. 6). The amplitude of slow shifts was ~100 μV. In patient 8, among eight seizures which had repetitive small EMG discharges only at the left tibialis anterior muscle (small seizure group), no seizures showed clear ictal shifts and only positive spikes were observed at Cz (Fig. 7A). However, among 20 seizures which had, around the clinical onset, a rapid development of EMG discharge at the left tibialis anterior muscle and simultaneous recruitment

Table 4 *Ictal EEG findings in three patients with NLE evaluated by scalp electrodes*

	Patient		
	7	8	9
No. of recorded seizures*	10	28	22
Symptoms at clinical onset†	Left hand tonic contraction	Left foot tonic contraction	Bilateral hands tonic contraction
Initial ictal EEG discharges‡	15 Hz middle amplitude rhythmic at Cz, C4	Positive spikes at Cz	20 Hz low amplitude rhythmic at Cz
Time to clinical onset	–1 s	–5 to +5 s	–3 s
Ictal DC shifts			
Number of seizures§	4	7	3
Polarity	Negative	Negative	Negative
Location	Cz, Fz and C4	Cz	Cz
Time to clinical onset	–1 s	–5 to +5 s	–3 s
Time to ictal EEG discharges	No difference	No difference	No difference
Incidence rate¶	40%	25%	14%

*Only seizures showing habitual clinical semiology were accepted. †Determined by the monitored EMG onset in patients 7–9 as described in the Patients and methods section. ‡Judged by the EEG displayed with LFF of 1.0 Hz as described in the Patients and methods section. §Judged by the EEG displayed with LFF of 0.016–0.05 Hz as described in the Patients and methods section. ¶Calculated by the number of seizures with clear ictal DC shifts in § divided by the total number of recorded seizures in *.

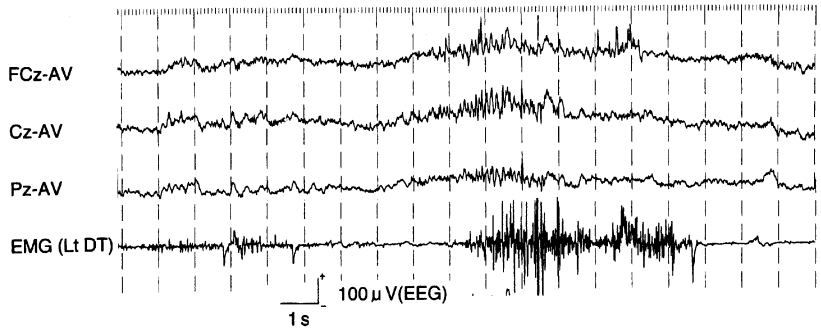

Fig. 6 Scalp-recorded ictal EEG recorded with LFF setting of 0.016 Hz in a simple partial seizure in patient 7 with right frontal lobe epilepsy. Clear negative shifts are observed at Cz, FCz and C4 (not shown in the figure) when 15 Hz middle amplitude rhythmic activity occurs at those electrodes. (DT = deltoid muscle, AV = averaged reference)

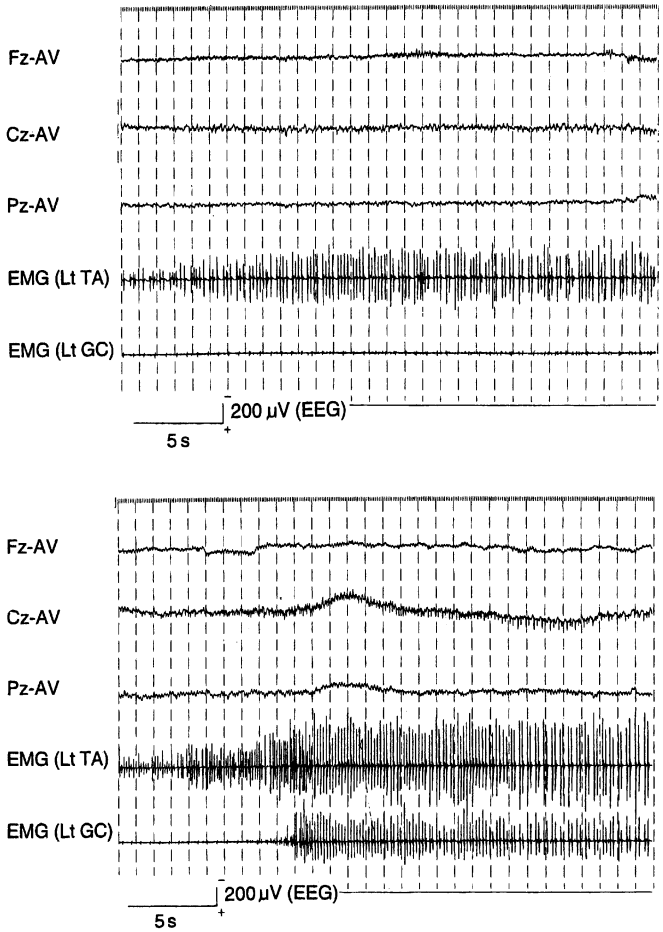

Fig. 7 Scalp-recorded ictal EEG recorded with LFF setting of 0.016 Hz in simple partial seizures (left foot motor seizures) in patient 8 with right parietal lobe epilepsy. (**A**) In a seizure which has repetitive small discharges only at the left tibialis anterior muscle (Lt TA), no ictal slow shifts but only the corresponding positive spikes are observed. (**B**) In a seizure which has, around the clinical onset, a rapid development of EMG discharge at the Lt TA and the simultaneous involvement of the left gastrocnemius muscle (Lt GC), clear negative slow shifts of 150–200 μV in amplitude are observed at Cz, Pz and FCz (not shown in the figure), where the repetitive spikes are also observed.

in the left gastrocnemius muscle (large seizure group) seven seizures showed clear negative slow shifts of 150–200 μV in amplitude at Cz and Pz where the repetitive spikes were also observed (Fig. 7B). In patient 9, small (50–75 μV) negative shifts were observed 1–3 s before the clinical onset as determined by the EMG onset of the right deltoid muscle. In all the three patients, those slow shifts were always surface-negative and were clearly superimposed by sustained 15–20 Hz fast activity in patients 7 and 9 and by repetitive spike discharges in patient 8. In none of the three patients was there clear difference of the onset time between the ictal slow shifts and the conventional ictal pattern.

Correlation of ictal DC shifts with histological finding and seizure control after resection

All six patients who were evaluated by subdural recording underwent selective cortical resection. The area to be resected was determined before surgery in each patient based upon both the conventional ictal EEG and the DC shift findings, and the functional mapping was also taken into account. Patients 1 and 5 had amygdalo-hippocampectomy, and patient 5, in addition to that, had the resection of the right posterior lateral, temporal cortex (2 × 2 cm in size), which generated slow shifts and middle amplitude fast activity as shown in Fig. 4. In patient 2, the right mesial frontal area (2 × 3 cm in size) was resected including the area corresponding to electrodes 3 and 5 (Fig. 1). In patient 3, a part of the right lateral premotor area, just anterior to the hand motor area, (2 × 3 cm in size) was resected. In patient 4, a part of the right precentral gyrus (1 × 2 cm in size) corresponding to the face sensorimotor area was resected. In patient 6, a part of the left postcentral gyrus and superior parietal lobule (3 × 4 cm in size), and the lower part of the left paracentral lobule (2 × 2 cm in size) were resected. The resected area in all the patients included the area of 'DC shifts', and it partly included the conventional EEG onset zone because the resected area was smaller than the conventional EEG onset zone.

All the patients were treated with no change in the

anticonvulsants for at least the initial 2 years after surgery, and the follow-up period ranged between 6 and 30 months (mean 18 months). Seizures were well controlled after surgery in all the patients; Engel's class I in two patients and class II in four (Engel *et al*., 1993). Among four patients with class II, seizures became less frequent while observed monthly following surgery. Histologically, two patients had dysplasia, two gliosis and one astrocytoma grade II. The resected hippocampi in two patients showed sclerosis.

With regard to the incidence rate of ictal DC shifts in relation to histological findings, patient 5 who had focal gliosis in the epileptogenic area showed the lowest incidence rate (42%) of ictal slow shifts. However, patient 2 who also had focal gliosis showed the highest (100%) incidence rate of slow shifts. At least among the six patients in the present study, there was no clear difference in the incidence rate of ictal DC shifts related to the histological finding.

Discussion

Subdural recording

It was clearly shown in the present study that subdurally recorded slow shifts (called DC shifts in this paper) were highly sensitive and specific for delineating an epileptogenic area. By using LFF of 0.016 Hz for the AC amplifier, slow ictal shifts were recorded in 85% of all the recorded seizures and they were localized in a more restricted area than the one defined by the conventional ictal EEG pattern. For each individual patient, the DC shifts were restricted to just one or two particular electrodes. As shown in Figs 1–5, the slow shifts were, in most cases, observed in the centre of the area which showed the conventional ictal EEG activity. Therefore, they most likely delineate highly specific epileptogenic areas. Luders *et al*. (1993) recently proposed different degrees of epileptogenicity in humans as a conceptual consideration. An epileptogenic zone is defined as the area which is necessary and sufficient for initiating seizures and whose removal or disconnection is necessary for abolition of seizures, and therefore, ictal onset zone could correspond to the epileptogenic zone. It is usually smaller than and is contained in the irritative zone which generates interictal spikes. In the present patients, the resected area was relatively small partly because the functional area at or just adjacent to the epileptogenic area was preserved as much as possible. It may be reflected in the fact that only two patients obtained the class Ia degree of seizure improvement (Engel *et al*., 1993). However, in four patients with class II improvement, seizures became gradually less frequent during the follow-up period after surgery. It was consistent with the 'running down phenomenon' described by Salanova *et al*. (1996). Since we resected at least the cortical area which generated ictal DC shifts, we postulate that the preserved irritative zone might have been more or less active immediately after the surgery, but could have run down afterwards. Therefore, it is most likely that the ictal DC shifts could have delineated at least a part of an epileptogenic area, but not the irritative zone.

In the previous paper, based on the results of three patients, we pointed out that slow ictal shifts were accompanied by an electrodecremental pattern (Ikeda *et al*., 1996). In the present study, five out of six patients clearly showed slow ictal shifts when the electrodecremental pattern appeared (Figs 1, 3, 4 and 5). Therefore, in a total of eight patients out of nine in our series, the DC shifts have a strong temporal relationship to the electrodecremental pattern. Only one patient (patient 3) (Fig. 2) showed the DC shift in association with about 1 Hz rhythmic activity instead of an electrodecremental pattern.

With regard to the onset time of ictal DC shifts with respect to the clinical onset, in our previous study (Ikeda *et al*., 1996) the ictal DC shifts preceded the clinical onset by 11–35 s in two patients, but in one patient (patient 1 in Ikeda *et al*., 1996) slow shifts occurred 32 s after the clinical onset (somatosensory aura), when 2–3 Hz spike activity was replaced by low amplitude, 30–40 Hz activity. In the present study, the slow ictal shifts preceded the clinical onset by 2–13 s in two patients, and they coincided in one patient. In one patient (patient 6), the ictal DC shift was observed 5–20 s after the clinical onset (right foot tonic posturing) when 2 Hz rhythmic activity was replaced by low amplitude fast activity. Therefore, five out of seven patients had the onset of ictal DC shifts no later than the clinical onset, and in the remaining two patients the slow ictal shift onset was later than the clinical onset. Thus, although the onset of ictal DC shifts is not necessarily earlier than the clinical onset, they do tend to precede the clinical onset simply because an electrodecremental pattern often occurs as the initial ictal EEG activity in human epilepsy as found also in experimental animal studies (Ayala *et al*., 1973).

Six patients in the present study varied in their histological diagnosis, as did the three patients in our previous study (Ikeda *et al*., 1996) who had cortical heterotopia, cystic tumour and cortical dysplasia. Although cortical dysplasia was seen only in three of the eight patients in total, ictal DC shifts were observed in all. Therefore, it is likely that slow ictal shifts represent a common epiletogenic feature regardless of histological findings in human epilepsy.

Among the six patients in whom the subdural recording was done, patient 1, who had MTLE, had subdural electrodes on the left mesial temporal structure covering the parahippocampal gyrus. It clearly showed the slow negative shifts superimposed on the 15 Hz middle amplitude activity. Therefore, slow ictal shifts are important for delineating the epileptogenic focus not only in the neocortical but also in limbic structures. In the study of ictal slow field potential in animals, Gloor *et al*. (1962) clearly demonstrated slow negative, ictal shifts from the hippocampus. However, since the present study only included one patient with MTLE, further work is warranted in this regard.

In patient 6, we used the subdural electrode with a diameter of 5 mm, in contrast to the usual size of 3 mm in the other patients. However, it did not make a significant difference to ictal slow potential in terms of onset time, amplitude and the

degree of extension, as judged from the waveform in patient 6. We pointed out the effect of electrode size on slow potential recording (Ikeda *et al*, 1998), suggesting that the larger recording contact is better. However, the present as well as our previous finding (Ikeda *et al*., 1996) may lead us to the conclusion that a subdural electrode with a diameter of at least 3 mm is sufficient to record slow potentials.

In summary, the present study extended our previous work on ictal DC shifts in humans as follows (Ikeda *et al*., 1996): subdural electrodes with a diameter of at least 3 mm consistently recorded ictal DC shifts of mainly negative polarity. The onset time was closely associated with the appearance of an electrodecremental pattern and it often preceded the clinical onset. They were observed only in one to two electrodes which also belonged to the area showing conventional ictal EEG change. These characteristics of DC shifts were common regardless of histological findings of the epileptogenic zone. The fact that resection of the area showing ictal DC shifts and one partly including the area showing conventional ictal EEG pattern resulted in favourable seizure control strongly suggests that ictal DC shifts are indicative of an epileptogenic zone more specifically.

Scalp recording

We successfully recorded focal, ictal slow shifts from scalp electrodes in all three patients studied. Compared with subdurally recorded ictal DC shifts, at least two different characteristics were observed as follows: first, scalp-recorded ictal DC shifts showed low sensitivity. The DC shifts were recorded in only 23% of all the seizures recorded from the three patients. However, in contrast to subdural recording, even the conventional ictal EEG pattern was not necessarily observed in all the seizures recorded by scalp recording, as in patient 9. This patient had SMA seizures clinically, and the conventional ictal EEG change, i.e. 20 Hz low amplitude fast activity, was observed in 53% of the recorded seizures with LFF setting of 1.0 Hz, and scalp-recorded, focal ictal slow shifts were observed only in 14% of the recorded 35 seizures with LFF setting of 0.016 Hz. In patients 7 and 8, the conventional ictal EEG change was observed in all the recorded seizures, and the ictal DC shifts were observed in 40% and 25% of the recorded seizures, respectively. Thus, at least in the present three patients, the more frequently the conventional ictal pattern was observed, the more often the ictal slow shifts were detected by scalp electrodes. Taking this tendency into account, low incidence rate of slow shift recording in patient 9 (14%) may not represent the true sensitivity of the scalp-recorded slow ictal shifts, but the values based on patients 7 and 8, 25–40%, might represent it better. However, more patients are needed for a definitive conclusion. With regard to the specificity, since scalp-recorded slow ictal shifts were localized in the same area as or in a more restricted area than the conventional ictal EEG change, they could be as specific as the subdurally recorded DC shifts.

Secondly, ictal DC shifts and seizure intensity seem to be correlated with each other (Fig. 7). In subdural recording, slow ictal shifts were invariably localized to only one to two electrodes regardless of seizure intensity. It is probably because the subdurally recorded slow shifts represent the activity of an epileptogenic, core area, and also because seizure intensity could reflect the degree of its subsequent extension and involvement from an original epileptogenic core area to the secondary or adjacent areas. In general, a certain scalp-recorded activity is derived from the simultaneously discharged cortical area of at least 6 cm^2 (Cooper *et al*., 1965). Therefore, the initial slow potential shift derived solely from an epileptogenic core activity, which is restricted to one to two subdural electrodes in the present study, may not necessarily be detected by scalp electrodes. Slow shifts detected by scalp electrodes could be the results of propagation or extension from the very initial ictal onset zone. It may explain the reason why the scalp-recorded ictal slow shifts depend on the seizure intensity, but is not necessarily the case in the subdurally recorded slow shifts. It is worthwhile mentioning that Chatrian and colleagues (Chatrian *et al*., 1968) documented that multiple or paroxysmal repetitive spikes such as those seen in generalized tonic seizures provoked minimal DC shifts in scalp recording in humans. However, they showed that discharges consisting primarily of slow waves with little spike component detectable by scalp recording were accompanied by a large negative shift. Therefore, they speculated that slow shifts accompanied by spike and wave complexes represent current flow to apical dendrites acting as passive sinks for hyperpolarizing current preferentially generated in the deeper cortical layer corresponding to slow wave activity. It may also explain the reason why the scalp-recorded electrodecremental pattern, consisting of only low voltage spike components produces low sensitivity of slow DC shifts and why slow DC shifts were infrequently seen in seizures of small intensity in the present study.

Scalp-recorded slow shifts, otherwise, had many common features to those detected by subdural recording: (i) mainly surface-negative in polarity; (ii) electrodecremental pattern in strong correlation to the appearance of slow ictal shifts; (iii) usually starting before the clinical onset; and (iv) clearly detected at least in patients with NLE.

When studying scalp-recorded ictal DC shifts in the present study, we only investigated the patients with NLE. Since subdurally recorded ictal DC shifts were closely related to the appearance of electrodecremental pattern (Gumnit and Takahashi, 1965; Ikeda *et al*., 1996), we did not study patients with MTLE in whom the scalp-recorded ictal pattern is usually 4–7 Hz rhythmic discharges rather than the electrodecremental pattern. Furthermore, since patients with MTLE usually present massive automatisms ictally, those movement artefacts would obscure the ictal slow shifts, even if present. This is one of the reasons why, in a patient with TLE in our previous study, only two out of 13 seizures showed the clear negative slow shifts on the scalp (Ikeda *et al*., 1997*a*). However, as shown in patient 3 and also in

patients with 3 Hz spike and slow wave complexes (Chatrian *et al*., 1968), slow ictal shifts were observed without electrodecremental pattern, but with low frequency rhythmic ictal discharges. Thus, scalp-recorded ictal slow shifts might be applicable for patients with MTLE. Nevertheless, movement artefacts could be one of the major factors to be overcome to achieve reliable scalp recording.

Pathophysiology of ictal DC shifts and clinical usefulness

DC shifts in epileptic seizures have been studied in penicillin-induced seizures (Gumnit and Takahashi, 1965). During seizures, sustained cellular depolarization in the epileptogenic centre generated slow negative potentials in the cortical surface. Glial cells in the same region may play a significant role in augmenting the small DC shifts because the concentration of extracellular potassium increases during the ictal event (Prince *et al*., 1973; Caspers *et al*., 1987). Glial cells are thus passively depolarized, resulting in large amplitude of slow shifts. With regard to the kindling phenomenon, maximal dentate activation elicited by amygdala stimulation is regarded to be strongly related to kindling. Maximal dentate activation is defined by the presence of a burst of a large amplitude population of spikes associated with a secondary rise in the extracellular potassium and negative shifts of DC potentials (Stringer and Lothman, 1992) Since it is a marker for reverberatory seizure activity (i.e. seizure amplification, in the hippocampal-parahippocampal circuits) associated ictal DC shifts could be a strong marker of the development of epileptogenesis. Recently it was shown that anoxic depolarization producing slow DC shifts is closely associated with a massive intracellular calcium elevation possibly due to activation of NMDA (*N*-methyl-D-aspartate) receptors, but it may not necessarily be enough to produce immediate, irreversible neuronal damage (Heinemann *et al*., 1977; Kral *et al*., 1993). Although the onset latency of anoxic depolarization studied *in vitro* was 3–5 min (Kral *et al*., 1993), the similar pathophysiology may also contribute to the generation of ictal DC shifts, especially of its late phase.

The subdurally recorded slow ictal shifts are clinically useful in strengthening the conventional ictal EEG finding and in confirming the epileptogenic area. In neocortical seizures even subdural recordings show widely distributed or ill-defined initial ictal change, especially when imaging studies did not reveal a clear focal abnormality (see Van Ness, 1992; Williamson *et al*., 1993). In addition, it would be difficult to judge the area most attenuated in amplitude from the electrodecremental pattern, which is usually seen as the initial ictal EEG changes in NLE. Ictal DC shifts, in contrast, are so prominent and transient that the areas which show the maximal changes of ictal DC shifts are easily recognized.

Little has been reported so far concerning the scalp-recorded ictal slow shifts in humans and their clinical usefulness still remains to be proven. Based on the findings in the three patients reported here and one previous patient of ours (Ikeda *et al*., 1997*a*), it is clearly worthwhile studying them further in patients with NLE rather than MTLE. However, when interpreting the results, caution should be paid to their low sensitivity and vulnerability to movement artefacts.

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