Ictal cerebral haemodynamics of childhood epilepsy measured with near-infrared spectrophotometry

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Summary
Near-infrared spectrophotometry (NIRS) is a new technique that allows continuous non-invasive monitoring of tissue oxygenation and haemodynamics in the brain. We used NIRS in various types of paediatric epileptic seizures in order to understand the pathophysiology of epileptic seizures in childhood epilepsy. This study examined 15 children ranging in age from 1.5 months to 16 years (nine males and six females), with different types of epilepsy. Six series of tonic spasms and 67 isolated seizures were recorded. The results demonstrated that several pathophysiological processes exist during ictal seizures in childhood. (i) Convulsive seizures were associated with a remarkable increase in cerebral blood volume (CBV), while absence seizures were associated with a mild decrease or no change in CBV of the frontal cortex. (ii) An initial transient decrease in CBV was observed in some types of convulsive seizures. (iii) An ictal increase in CBV changed to an ictal decrease in the course of tonic status epilepticus. (iv) There was definite heterogeneity in the CBV changes during tonic spasms in patients with West syndrome. NIRS is easily applicable to paediatric patients with epilepsy and may provide new insights into the pathophysiology of various types of epileptic seizure.

Keywords: near-infrared spectrophotometry; epilepsy; cerebral blood volume; cerebral blood flow; ictal monitoring

Abbreviations: CBF = cerebral blood flow; CBV = cerebral blood volume; CytO2 = oxidized cytochrome aa3; HbO2 = oxygenated haemoglobin; HbR = deoxygenated haemoglobin; LRE = localization-related epilepsy; PLE = parietal lobe epilepsy; NIRS = near-infrared spectrophotometry; rCBF = regional cerebral blood flow; SGT = secondary generalized tonic–clonic seizures; SPECT = single photon emission computed tomography; THb = total haemoglobin

Introduction
Recent advances in neuroimaging such as PET, single photon emission computed tomography (SPECT), magnetoencephalography and magnetic resonance spectrometry have improved seizure focus localization and understanding of the pathophysiology of epileptic foci. Ictal SPECT and PET show changes in cerebral blood flow (CBF) and metabolism during epileptic seizures (Engel et al., 1982, 1985; Bonte et al., 1983; Theodore et al., 1985; Chugani et al., 1994; Haginoya et al., 2001). Regional CBF (rCBF) and metabolism increase in the epileptogenic zone during partial seizures, but decrease interictally (Engel et al., 1982; Bonte et al., 1983; Chugani et al., 1994). However, ictal hypoperfusion of the epileptogenic zone has also been reported in some cases using SPECT. There is a controversy over the interpretation of this phenomenon. Avery and colleagues (Avery et al., 2000) reported that ictal SPECT injections made 90 s or more from seizure onset demonstrated focal areas of decreased rCBF at the epileptogenic site, while Lee and colleagues (Lee et al., 2000) reported focal ictal hypoperfusion only in cases in which the radiotracer was injected during the early ictal period. Thus, the perfusion changes of the epileptogenic zone during the peri-ictal period are not yet known exactly, since the information provided by such studies consists of static information obtained at a certain point during the peri-ictal or interictal period.

Near-infrared spectrophotometry (NIRS) is a new technique that allows continuous non-invasive monitoring of tissue oxygenation and haemodynamics in the brain. NIRS
measures changes in the concentrations of oxygenated haemoglobin (HbO₂), deoxygenated haemoglobin (HbR), and total haemoglobin (THb) (THb = HbO₂ + HbR). Assuming a constant haematocrit, changes in THb are used as an indicator of alteration in cerebral blood volume (CBV) (Cope et al., 1988). Simultaneous NIRS and PET measurements show that the changes in THb and HbO₂ correlate with changes in rCBF (Hoshi et al., 1994; Villringer et al., 1997). Several reports describe the potential of the NIRS technique for measuring haemodynamic changes related to human brain activity, including sensorimotor (Obrig et al., 1996), visual (Hoshi and Tamura, 1993), auditory (Hoshi and Tamura, 1993), cognitive (Chance et al., 1993) and language (Okada et al., 1993) activity.

However, there have been few reports in the literature of the application of NIRS to epileptic seizures (Steinhoff et al., 1996; Watanabe et al., 1998; Adelson et al., 1999). Recently, Watanabe and colleagues applied multichannel NIRS monitoring to measure bemegride-induced ictal changes in CBV in 10 patients with temporal lobe epilepsy and two patients with parietal lobe epilepsy (PLE) (Watanabe et al., 1998). The patients showed an ictal increase in CBV on the side of the epileptic focus and it was concluded that NIRS is one of the most reliable techniques for focus diagnosis. We used NIRS to examine various types of paediatric epileptic seizure in order to understand the pathophysiology of epileptic seizures in childhood epilepsy.

**Patients and methods**

This study examined 15 children, ranging in age from 1.5 months to 16 years (nine males and six females) with different types of epilepsy as listed in Table 1. Informed consent was obtained from the parents before each NIRS study. In total, six series of tonic spasms and 67 isolated seizures were recorded with NIRS. Tonic seizures were recorded in five patients [neonatal onset localization-related epilepsy (LRE), startle epilepsy, Lennox–Gastaut syndrome, secondary generalized epilepsy and West syndrome]. An asymmetrical generalized clonic seizure was observed in one patient with severe myoclonic epilepsy in infancy. Secondary generalized tonic–clonic seizures (SGT) and focal motor seizures were recorded in patients with LRE. We studied four patients with West syndrome who had hypersarrhythmia and typical tonic spasms with cluster formation. In three of these patients, we recorded tonic spasms; in the fourth, we recorded a brief tonic seizure that coexisted with tonic spasms. An epileptic spasm was recorded in one patient with band heterotopia. Complex partial seizures were recorded in four patients with neonatal onset LRE, PLE and band heterotopia. Absence seizures were monitored in two patients.

The NIRS system (NIRO300, Hamamatsu Photonics KK, Hamamatsu, Japan) used in this study produces light at four wavelengths (776, 810, 848 and 913 nm). The design and features of this device have been described previously (Suzuki et al., 1999). Light at each frequency is transmitted in sequential pulses by a fibre-optic cable (optode) to the patient’s forehead. The transmitting and receiving optodes are placed 4 cm apart on the patient’s forehead to detect haemodynamic changes in the frontal cortex. The difference between the transmitted and received light intensities at each wavelength is used to determine the optical density change at each wavelength. A computer converts the changes in optical density into changes in cerebral HbO₂, HbR, and concentration of oxidized cytochrome aa₃ (CytO₂) expressed in micromoles (µM). We did not include the CytO₂ data in this study because the in vivo spectrum and physiological meaning of changes in the redox state of cytochrome oxidase remain controversial (Cooper et al., 1994). The THb was calculated as the sum of HbO₂ and HbR, and was used as a measure of CBV. Changes in HbO₂, HbR and THb from an arbitrary zero were measured continuously from the pre-ictal through the post-ictal period in spontaneously occurring seizures. Measurements were made every 0.5 s. We applied a differential path length factor of 4.0 in patients less than 3 years of age (Benaron et al., 1990; van der Zee et al., 1992; Cooper et al., 1996) and 5.9 in patients older than 3 years of age (van der Zee et al., 1992). The optical path length was set by multiplying the interoptode distance by differential path length factor. An EEG was also recorded simultaneously in all but two patients (Cases 6 and 13). In the two exceptions, ictal EEGs were recorded separately within 2 days of the NIRS study. To avoid movement artifacts, the patient’s head was held to reduce movement as much as possible during seizures. Ictal records with extensive motion artifacts and unstable baseline levels were excluded from the analysis. Using t-tests, we compared sampling data for the ictal period with a pre-ictal period with the same amount of data as the ictal period. Significance was established at P < 0.05.

**Results**

**Generalized tonic–clonic seizure, tonic seizure, clonic seizure, focal motor seizure (Cases 1–7)**

The NIRS, ictal and interictal EEG, and neuroimaging studies are summarized in Table 1. The ictal NIRS classification is summarized in Table 2. Out of seven cases with convulsive seizures (which included SGT, tonic seizures, brief tonic seizures, asymmetrical generalized clonic seizures and focal motor seizures), an increase in THb, HbO₂ and HbR was observed in five cases (Fig. 1). An increase in THb and HbO₂ with no change in HbR was observed in one case, and a decrease in THb and HbO₂ with no change in HbR was observed in another. In Case 6 (with tonic status epilepticus), THb and HbO₂ increased early in the seizures and as in the other cases with convulsive seizures. However, both values gradually attenuated and then decreased in the later period (Fig. 2A–C). In four out of seven cases with convulsive seizures (Fig. 1) and in one with an epileptic spasm (Fig. 4B), a transient decrease in all three parameters was observed at
the onset of the seizure. The duration of the transient decrease ranged from 2 to 12 s.

Complex partial seizure (Cases 7–10)
Because the optodes are placed on the patient’s forehead, this method only detects changes in the frontal cortex. This was demonstrated to be true in Cases 7 and 8, which had complex partial seizures. A hypomotor seizure originating from the left parietal to occipital area in Case 7 and an electrical seizure originating from the left parietal area in Case 8 (Fig. 3B), whose ictal SPECT showed hyperperfusion of the right parietal lobe, did not produce any change in the NIRS parameters before propagation of the epileptic activity from the focus. Case 9, however, whose optodes were placed on the right forehead, showed an ictal increase in THb and HbO2. The ictal SPECT in Case 9 showed hyperperfusion of the right frontal to parietal areas. A patient with band heterotopia had a complex partial seizure and an epileptic spasm. The ictal EEG failed to localize the seizure focus; however, our preliminary magnetoencephalography study showed a dipole location in the parietal inner heterotopic layer. Both types of attack elicited an ictal increase in THb and HbO2 in the frontal lobe, where the optodes were placed (Fig. 4). These results differ from those for other patients with complex partial seizures (Cases 7 and 8), suggesting that seizure propagation in band heterotopia differs from that in other types of LRE.

Absence seizure (Cases 11 and 12)
In absence seizures, observed in two patients, one patient showed no substantial changes in the three parameters, which were reproducibly recognized. However, another patient with atypical absence showed a small, but significant, decrease in THb and HbO2, while HbR increased during all the five seizures examined (Fig. 5). These two patients also showed frequent generalized spike-wave bursts on EEG without absence seizures, during which no changes in NIRS parameters were observed.

Tonic spasms (Cases 13–15)
One of three patients with West syndrome showed a remarkable increase in all three parameters during spasms (Fig. 6), while the remaining two patients showed no substantial changes. The ictal EEG showed generalized irregular polyspike-waves in Case 13, generalized fast waves in Case 14 and generalized delta waves in Case 15. The clinical difference between Case 13, and Cases 14 and 15 seems to be the strength of the spasms. Very strong contractions of the extremities were observed in Case 13, while the other two patients had very mild spasms. In Case 13, we immobilized the patient’s head during spasms to eliminate motion artifact. Hypsarrhythmia that appeared continuously during periods of wakefulness and periodically during sleep did not produce any changes in the three parameters.

Discussion
CBV changes during seizures and NIRS
Based on the current understanding of the coupling of neuronal activation and CBF, it is widely accepted that localized activation of neuronal populations leads to a fast, localized increase in blood flow in a restricted cortical area (Villringer and Dirnagl, 1995). An increase in THb can be induced by either an increase in rCBF, which is usually associated with an increase in HbO2, or by obstruction of the cerebral venous return, such as with crying, which is usually associated with an increase in HbR (Brazy, 1988) or by a combination of these factors. In a human activation study of adults using NIRS, researchers demonstrated a decrease in HbR with increases in both HbO2 and THb in the area of activation (Chance et al., 1993; Hoshi and Tamura, 1993; Okada et al., 1993; Obrig et al., 1996). This was interpreted as an increase in cerebral blood supply exceeding the increase in neuronal oxygen consumption responsible for the production of deoxyhaemoglobin (Malonek and Grinvald, 1996; Obrig et al., 1996). In the activated area of animal brains, oxygen consumption causes an early (<3 s) increase in HbR and then a reactive increase in regional perfusion, which occurs >1 s after the increase in HbR. This results in a rise in HbO2 and a decrease in HbR due to washout (Malonek and Grinvald, 1996; Malonek et al., 1997). The relative contribution of oxygen consumption and blood supply determines whether HbR increases or decreases. Contrary to the activation study of adults, photic stimulation of early infants revealed concomitant increases in HbR and HbO2 in the occipital lobe, which were demonstrated using NIRS (Meek et al., 1998) and functional MRI (Yamada et al., 2000). These findings suggest that maturation of the brain affects neuronal oxygen consumption and cerebral blood supply. As in activation studies, focal seizures elicit an increase in rCBF in the seizure focus by decreasing cerebrovascular resistance, which is mediated by local tissue changes, such as changes in nitric oxide (Iadecola, 1992), pH and CO2 (Lassen, 1968) and adenosine (Berne et al., 1974). However, the propagation of seizure activity to subcortical systems induces mass excitation of the sympatno-adrenal axis (Doba et al., 1975) and brain stem centres affecting autoregulation (Langfitt and Kassell, 1968; Reis, 1984), resulting in a remarkable change in CBF (Meldrum and Nilsson, 1976).

Although our method is limited, in that it only measures changes in THb, HbO2 and HbR in the frontal cortex, the results demonstrate that several pathophysiological processes exist during epileptic seizures in childhood.

(i) Convulsive seizures were associated with a remarkable increase in CBV, while absence seizures were associated with a mild decrease or no change in the CBV of the frontal cortex.

(ii) Initial transient decreases in CBV and HbR were observed in some types of convulsive seizures.

(iii) An ictal increase in CBV changed to an ictal decrease in the course of tonic status epilepticus.
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age at NIRS</th>
<th>Clinical summary</th>
<th>Diagnosis</th>
<th>Seizure type recorded with NIRS</th>
<th>Interictal EEG</th>
<th>Ictal EEG</th>
<th>Neuroimaging</th>
<th>Total number of seizures recorded</th>
<th>NIRS findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>10 years</td>
<td>At age 8 years, onset of seizures with asymmetrical generalized tonic–clonic convolution with slight dominancy over left extremities; seizure status once a month; IQ within normal range</td>
<td>Right LRE</td>
<td>SGT</td>
<td>Rare spikes in right frontal</td>
<td>See Fig. 1B</td>
<td>Interictal SPECT: global hypoperfusion over right hemisphere. MRI: normal</td>
<td>1</td>
<td>See Fig. 1A</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>7 years</td>
<td>At age 3 weeks, intracranial haemorrhage due to vitamin K deficiency; received neurosurgical drainage. Since then spastic quadriplegia, severe mental retardation and intractable focal motor seizure developed. At age 5 years, seizure type changed to generalized tonic seizure frequently elicited by sound stimuli</td>
<td>Startle epilepsy</td>
<td>Tonic seizure</td>
<td>Multifocal spikes</td>
<td>Generalized fast waves</td>
<td>CT scan: severely atrophied both hemispheres</td>
<td>1</td>
<td>A sound elicited a tonic seizure lasting ~30 s. In the first 5 s, all three parameters decreased; this was followed by increases in THb and HbO2.</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>6 years</td>
<td>Since age 4 months, febrile and afebrile unilateral convolution developed. Since age 5 years, seizure frequency increased up to 50 times a month. At present, patient has delayed psychomotor development (DQ: 55) and occasional myoclonic movement of right arm</td>
<td>Severe myoclonic epilepsy in infancy</td>
<td>Asymmetric generalized clonic convolution</td>
<td>Multifocal sharp waves and spike-waves in left anterior temporal–prefrontal, left central–parietal–posterior temporal</td>
<td>Spike-waves over left hemisphere during right-sided asymmetrical generalized clonic seizure</td>
<td>MRI: normal</td>
<td>Intercitial SPECT: normal</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>4 years</td>
<td>Full term vacuum delivery. Treated as West syndrome at age 9 months, but failed. At present, severe development delay without head control; brief tonic seizures appear daily; atarthrosplastic quadriplegia exists</td>
<td>Secondary generalized epilepsy</td>
<td>Brief tonic seizure</td>
<td>Diffuse spindle-like fast waves</td>
<td>Diffuse alpha burst or high voltage slow waves followed by fast waves</td>
<td>MRI: severe cortical atrophy</td>
<td>11</td>
<td>Increase in all three parameters</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>6 months</td>
<td>At age 5 months, spasms appeared with series formation; brief tonic seizure also observed on admission at age 6 months, well controlled by ACTH</td>
<td>West syndrome</td>
<td>Brief tonic seizure</td>
<td>Hypsarrhythmia</td>
<td>Generalized fast waves</td>
<td>MRI: mild cortical atrophy. Intercitial SPECT: normal</td>
<td>1</td>
<td>Abrupt decrease in THb and HbO2, while no change of HbR</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>13 years</td>
<td>At age 3 months, developed West syndrome. At age 6 years, seizure type changed to tonic seizure and atypical absence with slow spike-waves complex. Since then, treated as Lennox–Gastaut syndrome; frequent episodes of tonic seizure status. At age 9 years, admitted for treatment of tonic seizure status</td>
<td>Lennox–Gastaut syndrome</td>
<td>Tonic seizure status</td>
<td>Frequent spikes in both occipital, independently</td>
<td>Generalized desynchronisation after diffuse single spike-waves, followed by fast wave burst</td>
<td>MRI: diffuse cortical atrophy</td>
<td>15</td>
<td>See Fig. 2A–C</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>1.5 months</td>
<td>Full term vacuum delivery, asphyxia, intractable seizure occurred since fifth day after birth. Patient showed two seizure types: type A—eye deviation to left or right with tonic seizure lasting for 30 s; type B—phasic flexion of upper extremities and eye deviation accompanied with hypomotor phenomenon. At present, patient has severe developmental delay</td>
<td>LRE (neonatal onset)</td>
<td>Type A: tonic seizure; Type B: hypomotor seizure</td>
<td>Frequent, multifocal high voltage spikes; spike-waves and sharp waves in right central–parietal–occipital, left parietal–occipital</td>
<td>Type A: single spike over right hemisphere followed by diffuse desynchronisation dominant over right hemisphere; lasted for 10 s. Type B: fast spike bursts in left parietal–occipital for 20–30 s, followed by irregular α to θ waves</td>
<td>CT scan: multifocal, low density areas in the white matter</td>
<td>Type A: 4. Type B: 8</td>
<td>Type A: preictal decrease in three parameters for a few sec. followed by ictal increase in three parameters, especially THb and HbO2. Type B: ictal NIRS showed no change of three parameters when the optode was placed on the centre of patient’s forehead</td>
</tr>
<tr>
<td>Patient number</td>
<td>Sex</td>
<td>Age at NIRS</td>
<td>Clinical information</td>
<td>Diagnosis</td>
<td>Seizure type recorded with NIRS</td>
<td>Interictal EEG</td>
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<td>Neuroimaging</td>
<td>Total number of seizures recorded</td>
<td>NIRS findings</td>
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<tr>
<td>8</td>
<td>Male</td>
<td>9 years</td>
<td>Full term caesarean delivery; no asphyxia; delayed early development. At age 1.5 years, focal motor seizure appeared 40-60 times a month without control. At age 9 years, admitted for treatment of frequent complex partial seizures that consisted of left or right hemiconvulsion with secondary generalization. At present, patient has severe developmental delay (IQ &lt;20), visual and auditory disturbance, and choreoathetosis.</td>
<td>PLE (symptomatic)</td>
<td>Complex partial seizure</td>
<td>Multifocal spikes in right parietal–occipital and left parietal–occipital</td>
<td>Focal spike bursts originated from right parietal and sometimes from left parietal, then propagated to contralateral parietal area</td>
<td>CT and MRI: atrophy of cerebral cortex, especially frontal lobe, arachnoid cyst in right temporal fossa. Ictal SPECT obtained during left hemiconvulsion: hyperperfusion of right parietal lobe</td>
<td>5</td>
<td>See Fig. 3B, central</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>13 years</td>
<td>At age 6 years, seizure developed 1 year after surgery for congenital heart disease. At present, intractable complex partial seizures appear weekly and there is moderate mental retardation</td>
<td>Right PLE</td>
<td>Complex partial seizure</td>
<td>Sporadic spikes in right central–parietal</td>
<td>Diffuse fast wave bursts</td>
<td>MRI: normal. Ictal SPECT: hyperperfusion of right parietal–frontal</td>
<td>6</td>
<td>Gradual increase in THb and HbO₂, while no change in HBR</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>16 years</td>
<td>At age 4 years, first seizure appeared; at age 8 years, diagnosed as band heterotopia with epilepsy by EEG and MRI; IQ: 43; showed multiple type of seizures including epileptic spasm, complex partial seizure and brief tonic seizure. At present, seizures not controlled</td>
<td>Band heterotopia</td>
<td>Type A: complex partial seizure with automatism; Type B: head-nodding spasm</td>
<td>Frequent sharp waves in mid-parietal–both occipital</td>
<td>Type A: generalized α-range activity followed by low amplitude fast waves. Type B: generalized, single and high voltage sharp wave</td>
<td>MRI: typical band heterotopia. Interictal SPECT: equal perfusion pattern between inner and outer cortex</td>
<td>Type A: 1. Type B: 3</td>
<td>See Fig. 4A and B</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>3 years</td>
<td>Onset of myoclonic seizures of neck or upper extremities at age 3 years; GTCs and atypical absence are also recognized with video–EEG monitoring; subnormal intelligence</td>
<td>Myoclonic–astatic epilepsy</td>
<td>Atypical absence</td>
<td>Generalized spike-waves, focal spikes in right parietal</td>
<td>See Fig. 5B</td>
<td>MRI and CT: normal. Interictal SPECT: normal</td>
<td>5</td>
<td>See Fig. 5A</td>
</tr>
<tr>
<td>12</td>
<td>Female</td>
<td>6 years</td>
<td>At age 6 years, brief loss of consciousness occurred; subnormal intelligence; well controlled by clonazepam</td>
<td>Childhood absence epilepsy</td>
<td>Typical absence</td>
<td>Generalized 3 Hz spike-waves</td>
<td>Generalized 3 Hz spike-wave burst</td>
<td>MRI: arachnoid cyst at right temporal pole</td>
<td>5</td>
<td>No change of three parameters</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>6 months</td>
<td>Full term caesarean delivery due to foetal distress; at age 5 months, tonic spasms appeared, mild developmental delay at admission; well controlled by ACTH. At present, patient has mild developmental delay</td>
<td>West syndrome</td>
<td>Tonic spasms</td>
<td>Hypsarrhythmia</td>
<td>Generalized irregular spike-waves</td>
<td>MRI and CT: normal. Interictal SPECT: hyperperfusion of left temporal–parietal</td>
<td>1 series</td>
<td>See Fig. 6A and B</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>6 months</td>
<td>At age 2 months, partial seizure with right parietal spikes; changed to hypsarrhythmia and tonic spasms at age 5 months; well controlled by ACTH. At present, patient has mild developmental delay</td>
<td>West syndrome</td>
<td>Tonic spasms</td>
<td>Hypsarrhythmia</td>
<td>Generalized fast waves</td>
<td>MRI and CT: mild cortical atrophy. Interictal SPECT: hyperperfusion of bilateral frontal cortices</td>
<td>4 series</td>
<td>No change of three parameters</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>7 months</td>
<td>Full term normal delivery; at 6 months, tonic spasms appeared. At present, spasms are controlled by ACTH; mild developmental delay exists</td>
<td>West syndrome, NF1</td>
<td>Tonic spasms</td>
<td>Hypsarrhythmia</td>
<td>Generalized high voltage slow waves</td>
<td>CT: normal. Interictal SPECT: hyperperfusion of bilateral basal ganglia</td>
<td>1 series</td>
<td>No change of three parameters</td>
</tr>
</tbody>
</table>

ACTH = adrenocorticotropic hormone; GTC = generalized tonic-clonic seizures; NF1 = neurofibromatosis type 1.
Table 2 Results of the ictal NIRS

<table>
<thead>
<tr>
<th>Case</th>
<th>Diagnosis</th>
<th>Seizure type</th>
<th>Classification of NIRS findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right LRE</td>
<td>SGT</td>
<td>A*</td>
</tr>
<tr>
<td>2</td>
<td>Startle epilepsy</td>
<td>Audiogenic tonic seizure</td>
<td>B*</td>
</tr>
<tr>
<td>3</td>
<td>SMEI</td>
<td>Asymmetrical clonic seizure</td>
<td>A</td>
</tr>
<tr>
<td>4</td>
<td>SGE</td>
<td>Brief tonic seizure</td>
<td>A</td>
</tr>
<tr>
<td>5</td>
<td>West syndrome</td>
<td>Brief tonic seizure</td>
<td>E</td>
</tr>
<tr>
<td>6</td>
<td>Lennox–Gastaut syndrome</td>
<td>Tonic seizure status</td>
<td>A*–B*–E</td>
</tr>
<tr>
<td>7</td>
<td>LRE (neonatal onset)</td>
<td>Tonic seizure</td>
<td>A*</td>
</tr>
<tr>
<td>8</td>
<td>PLE (symptomatic)</td>
<td>CPS</td>
<td>B</td>
</tr>
<tr>
<td>9</td>
<td>Right PLE</td>
<td>CPS</td>
<td>B</td>
</tr>
<tr>
<td>10</td>
<td>Band heterotopia</td>
<td>CPS</td>
<td>B</td>
</tr>
<tr>
<td>11</td>
<td>Myoclonic–astatic epilepsy</td>
<td>Atypical absence</td>
<td>E</td>
</tr>
<tr>
<td>12</td>
<td>Childhood absence epilepsy</td>
<td>Absence</td>
<td>D</td>
</tr>
<tr>
<td>13</td>
<td>West syndrome</td>
<td>Tonic spasms</td>
<td>A</td>
</tr>
<tr>
<td>14</td>
<td>West syndrome</td>
<td>Tonic spasms</td>
<td>D</td>
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<tr>
<td>15</td>
<td>West syndrome</td>
<td>Tonic spasms</td>
<td>D</td>
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A: increase in HbO₂, HbR and THb. B: increase in HbO₂ and THb, no change in HbR. C: increase in HbO₂ and THb, decrease in HbR. D: no changes in HbO₂, HbR and THb. E: decrease in HbO₂ and THb, no change in HbR. *Initial transient decrease. CPS = complex partial seizure; SMEI = severe myoclonic epilepsy in infancy

Fig. 1 Ictal NIRS and EEG of a secondary generalized tonic–clonic seizure in Case 1 with localization-related epilepsy. (A) Abrupt decreases in all three parameters (THb, HbO₂ and HbR) were observed at the onset of a seizure. All three parameters recovered to baseline after 12 s, then showed a remarkable increase that lasted as long as 2 min after cessation of the seizure. (B) Generalized bursts of spikes followed by spike-waves were recorded. The ictal discharges appeared slightly earlier in the right hemisphere.
There was definite heterogeneity in the CBV changes during tonic spasms in patients with West syndrome. Simultaneous ictal SPECT may be of help in verifying the efficacy of ictal NIRS recording more precisely.

**NIRS findings during convulsive seizures**

The ictal NIRS of convulsive seizures demonstrated that there were different patterns of ictal haemodynamics among patients. It is still unclear whether these differences reflect different patterns of propagation of seizure activity from the seizure focus or differences in neuronal activity in the frontal cortex during seizures. The patterns included: (i) increases in THb and HbO₂ associated with an increase in HbR; (ii) increases in THb and HbO₂ without a change in HbR and (iii) decreases in THb and HbO₂ without a change in HbR.

The increases in HbO₂ and THb could be caused by an increase in rCBF in the frontal cortex. On the other hand, an increase in HbR could be interpreted in two ways: either tissue oxygen consumption during seizures is much greater than that during activation studies, so that the reactive increase in cerebral blood supply is insufficient to wash out the deoxyhaemoglobin; or increased impedance of cerebral venous return during the seizure causes the increase. Both factors may be relevant, especially the former in infancy, according to the results of an activation study (Meek et al., 1998). Moreover, it is notable that the increase in rCBF was much greater than that seen in activation studies (Sakatani...
et al., 1999). Contrary to previous cases, the ictal decrease in CBV was seen in an infant with West syndrome during a brief tonic seizure. This may reflect the steal phenomenon caused by an epileptic focus located outside the frontal cortex. The steal phenomenon was recently demonstrated (Hollo et al., 2001) using subtraction SPECT in infants with occipital lobe epilepsy; concomitant ictal hypoperfusion was observed around the hyperperfused occipital area or the extra-occipital area when radiotracer was injected during the early ictal period.

In four out of seven cases with convulsive seizures and in one with an epileptic spasm, transient decreases lasting a few seconds were observed in all three parameters at the onset of a seizure. This probably reflected a decrease in CBV, together with a decrease in oxygen consumption. Surprisingly, in Case 1, there was an initial decrease of CBV lasting 12 s after the appearance of the generalized convulsion. A transient decrease in CBV has been observed using NIRS in seizures evoked by transcerebral electroshock in experimental animals (Kreisman et al., 1983) and in the seizures associated with electroconvulsive therapy in man (Saito et al., 1995). Experimental studies have shown that electrical stimulation of a complex nucleus of the dorsal pons can reduce rCBF by vasoconstriction, with or without parallel changes in metabolism (Reis, 1984). The propagation of seizure activity in these areas may cause a transient decrease in CBF, as recorded in the current study. A few seconds later, the mass excitation of the sympatho-adrenal axis leads to a remarkable increase in CBF (Doba et al., 1975). Alternatively, the transient steal phenomenon may redistribute CBV in accordance with the neuronal demand of the epileptogenic zone outside the frontal lobe as demonstrated using SPECT (Hollo et al., 2001).

**CBV changes during status epilepticus**

Status epilepticus leads to neuronal cell damage that is localized to selectively vulnerable regions, chiefly the cerebral cortex, cerebellum and hippocampus (Meldrum and Brierley, 1973). Experimental studies have revealed that there is a mismatch between rCBF and the metabolic rate in these vulnerable areas (Meldrum and Nilsson, 1976; Siesjo et al., 1983). In studies by Kreisman and colleagues (Kreisman et al., 1981, 1983), early seizures were accompanied by increases in CBV, arterial blood pressure, cortical oxygen pressure and Cyto2 pressure, indicating that oxygen supply was adequate to meet the metabolic demand of the

![Fig. 4 Ictal NIRS of a complex partial seizure (A) and an epileptic spasm (B) seen in Case 10 with band heterotopia. (A) No response and automatism of both hands were observed for 30 s. Abrupt increases in THb and HbO2 were observed, while no change in HbR was seen. (B) Epileptic spasm. Abrupt increases in THb and HbO2 were observed, while there was no change in HbR. Initial and transient decreases in all three parameters that lasted 1–2 s were noted. The THb and HbO2 returned to baseline levels 50 s after the spasm. Arrow indicates the occurrence of spasm.](image-url)
seizures. However, these variables failed to increase during subsequent seizures, resulting in decreases in CBV, cortical oxygen pressure and CytO₂, as occur in cerebral hypoxia (Kreisman et al., 1981, 1983). In Case 6, a patient with tonic status epilepticus, CBV increased early in the seizure as in the other cases with convulsive seizures; however, the CBV increase gradually attenuated and then decreased later in the seizure. These findings suggest that there is a transition from sufficient to insufficient cerebral oxygen supply during recurrent seizures, although we did not evaluate cortical oxygen pressure or CytO₂. Continuous monitoring with NIRS during status epilepticus may provide useful information on its deleterious effects.

CBV changes during absence seizures

The ictal changes in cerebral metabolism and CBF during absence seizures are still controversial. A study using H₂¹⁵O-PET, in which the data acquisition time was improved to ≤30 s, showed a 14.9% mean global increase in CBF associated with a relatively higher increase in the thalamus during absence seizures (Prevett et al., 1995). On the other hand, researchers using transcranial Doppler sonography and laser Doppler flowmetry observed a decrease in CBF during human absence seizures and in the genetic absence epilepsy rat (Sanada et al., 1988; Klingelhofer et al., 1991; Bode, 1992; Nehlig et al., 1996). In our study, one patient showed no substantial changes in CBV, while another showed a mild decrease in CBV during absence seizures. Gloor (1978) suggested that generalized spike-waves represent an abnormal response of cortical neurones to afferent thalamocortical projection; short periods of increased cortical excitation corresponding to the EEG spike are followed by a longer period of cortical inhibition, corresponding to the wave component. According to this hypothesis, CBF may decrease due to reduced cerebral neuronal activity during absence.

Fig. 5 Ictal NIRS and EEG of an atypical absence seizure in Case 12 with myoclonic-astatic epilepsy. (A) A small, but significant decrease in the THb and HbO₂ was recorded while HbR increased during the seizure. (B) Irregular slow spike-wave bursts were dominant over both frontal regions during the seizure.
seizures when the duration of inhibition of neuronal activity exceeds that of excitation, or may show no change when inhibition and excitation of neuronal activity are balanced.

CBV changes during tonic spasms of West syndrome

Despite extensive work by many investigators, the pathophysiology of West syndrome is still elusive. We have reported ictal SPECT studies of West syndrome, in which we found two clear ictal SPECT patterns: (i) focal cortical hyperperfusion; and (ii) a diffuse pattern that probably included patients with diffuse hyperperfusion and those with no changes (Haginoya et al., 2001). As one explanation of these heterogeneous ictal SPECT findings, we propose that the tonic spasms of West syndrome do not involve a single neurophysiological process, and that West syndrome is divided into subgroups defined by the origin of the spasms. In one group, the spasms originate in the cortical hemisphere (Gaily et al., 1995), while in other groups they originate in other structures such as the brainstem (Haginoya et al., 2001). In the current study, one of three patients with West syndrome showed a remarkable increase in all three parameters (THb, HbO2 and HbR concentrations) during spasms. Interestingly, the changes developed shortly before the onset of spasms.

Since the ictal EEG changes preceded the clinical onset of spasms in this patient by 60–70 s, we believe that the changes in the NIRS parameters shortly before the onset of spasms reflect neuronal activity associated with ictal EEG. It needs to be clarified whether differences in ictal NIRS patterns reflect differences in the neurophysiological or propagating processes as suggested in our SPECT study (Haginoya et al., 2001). Brain stem involvement might cause a phasic increase in CBV associated with each spasm, since cerebral vasodilation produced by brainstem stimulation has been described (Langfitt et al., 1968; Reis, 1984). Alternatively, ictal EEG may help to explain the heterogeneity of ictal NIRS; a patient with no changes on NIRS monitoring showed fast waves predominantly over the bilateral parieto-occipital areas during spasms. If the ictal perfusion changes are restricted to those regions, it is reasonable that NIRS optodes placed on the forehead would not detect changes in the frontal area. It is important to study more patients with West syndrome in order to clarify ictal change during NIRS monitoring.

References


Fig. 6 Ictal NIRS of tonic spasms in Case 13 with West syndrome. Abrupt increases in all three parameters were observed shortly before the onset of spasms (A). All three parameters showed a phasic increase corresponding to each spasm (B). Increases in the three parameters continued for at least 5 min after the cessation of spasms (A). Arrowheads indicate spasms.

References


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