

Epileptic encephalopathy with continuous spikes and waves in the occipito-temporal region during slow-wave sleep in two patients with acquired Kanji dysgraphia

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ABSTRACT – We encountered two patients with acquired Kanji dysgraphia in whom continuous spikes and waves, dominant in the occipito-temporal region, were recorded during slow-wave sleep. Electrical status epileptics during sleep (ESES) was demonstrated on overnight electroencephalography, and dipoles clustered in and around the posterior inferior temporal cortex on magnetoencephalography. Functional neuroimaging suggested dysfunction in the left posterior temporal lobe, including the posterior inferior temporal cortex. The patients had normal intelligence with no problems in reading and writing Kana, as well as copying, reading aloud, and identifying Kanjis, but showed Kanji dysgraphia (morphological, phonemic, and semantic error) accompanied by impaired visual processing. ESES was resolved by sodium valproate, clonazepam, and acetazolamide in Patient 1, and by adrenocorticotrophic hormone, sodium valproate, and clonazepam in Patient 2. The present cases had the unique cognitive dysfunction of Kanji dysgraphia, which is distinct from that of Landau-Kleffner syndrome and continuous spikes and waves during slow-wave sleep. However, the present cases also share common features with these two encephalopathies in terms of the clinical course, pathophysiology, neuroimaging, and response to steroids and antiepileptic drugs. In the context of the Japanese language, acquired Kanji dysgraphia may occur due to electrical dysfunction of left posterior inferior temporal cortex in patients with ESES.

Key words: CSWS, epileptic encephalopathy, ESES, Kanji dysgraphia, posterior inferior temporal cortex

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The epilepsy syndrome showing continuous spikes and waves (CSW) during slow-wave sleep is collectively classified under electrical status epileptics during sleep (ESES). Thus, ESES is age-dependent epileptic encephalopathy represented by Landau-Kleffner syndrome (LKS) and continuous spikes and waves during slow-wave sleep (CSWS) (Tassinari *et al.*, 2009). Intellectual regression and abnormal behaviour appear during ESES in many cases; acquired aphasia associated with auditory agnosia develops in LKS and intellectual regression occurs in CSWS.

Japanese is a complex language because it comprises two written languages: Kanji (morphograms) and Kana (syllabograms). The characteristics of these have been reported in detail by Iwata (Iwata, 1984). In summary, Kana is a phonogram similar to the alphabets of European languages and is morphologically simple, whereas Kanji is an ideograph, strongly related to meaning and the pronunciation varies with the situation. The morphology is complex and letters consist of several parts. The cognitive functions involved in Kanji and Kana writing are mediated via different processing pathways, and the posterior inferior temporal cortex (PITC), thalamus, and parietal lobe are reported to be involved in the Kanji system (Sakurai *et al.*, 2000; Usui *et al.*, 2005). Herein, we report two patients with acquired Kanji dysgraphia, in whom continuous spikes and waves (CSW), dominant in the occipito-temporal region, were recorded during slow-wave sleep.

Case studies

Patient 1 was a right-handed boy who had onset of generalized tonic-clonic seizures during sleep at 10 years and 3 months of age, and was admitted for detailed work-up. At the same time of seizure onset, errors in Kanji writing tests, performed monthly at school, increased. On overnight electroencephalography (EEG), generalized 1-2-Hz CSW, dominant in the occipito-temporal region, were recorded, and the spike-wave index was higher than 85% (*figure 1*). Magnetoencephalography (MEG) revealed dipoles clustering in and around the PITC (*figure 1*). Brain MRI was normal. On cerebral blood flow (CBF) SPECT and ¹²³I iomazenil SPECT, reduced uptake was noted in the left posterior temporal lobe, including the PITC. Treatment with sodium valproate, clonazepam, and acetazolamide markedly decreased CSW. Four months were required to control ESES, although spikes remained in the left occipital region. At 16 years of age, EEG was normalized, and clinical seizure and epileptic discharge did not recur even without antiepileptic drugs.

Neuropsychological testing was performed at 10 years and 3 months of age. On the Japanese Wechsler

Intelligence Scale for Children (WISC)-Revised, the full, verbal, and performance IQs were 95, 101, and 91, respectively. Scores for the Illinois Test of Psycholinguistic Abilities (ITPA), Benton Visual Retention Test (BVRT), Raven's Colored Progressive Matrices, Rey-Osterrieth Complex Figure Test (ROCFT), Developmental Test of Visual Perception (DTVP), and Visual Perception Test for Agnosia (VPTA), which do not require Kanji writing, were consistent with his age. He had excellent scores in Kanji writing tests at school before the onset of ESES. At the time of study, he had no problems in reading Kana, converting written Kanjis to Kana, and dictating in Kana after listening to a word. We performed Kanji recognition tasks as follows: copying a written Kanji from among several Kanjis, identifying the correct Kanji that matches a word written in Kana; and reading aloud a Kanji. Moreover, the Kanji writing tasks consisted of converting a word written in Kana to Kanji, and dictating in Kanji after listening to a word (*figure 2*). He had no problems in copying, reading aloud, and identifying Kanjis. However, his correct answer rates in Kanji writing tasks for third-(eight-year-old) and fourth-(nine-year-old) grade school children were 30 and 0%, respectively. His Kanji dysgraphia consisted of morphological, phonemic, and semantic errors (*figure 2*). In addition to medications, the patient also underwent educational interventions in an attempt to reinforce memorization of Kanjis, such as describing out loud how the strokes are made while writing each Kanji, and construction of Kanjis using the radicals (elements of the characters). Kanji dysgraphia ameliorated gradually several years after CSW was controlled, but he remained weak in his ability to write Kanji at high school.

Patient 2 was a right-handed boy who had a history of febrile convulsions without epileptic discharge on EEG at four years of age. Focal seizures with impaired consciousness occurred at seven years. Frequent interictal focal epileptic discharges were recorded in the left occipito-temporal region, indicating focal epilepsy. The seizures were controlled by carbamazepine, but frequent focal spikes in the same region persisted on annual EEGs. At 11 years of age, Kanji dysgraphia developed. Generalized CSW, dominant in the occipito-temporal region, were recorded and the spike-wave index was approximately 70% on overnight EEG (*figure 1*). MEG revealed clustering of dipoles in and around the PITC (*figure 1*). Brain MRI was normal. On CBF SPECT and ¹²³I iomazenil SPECT, reduced uptake was noted in the left posterior temporal lobe, including the PITC. Carbamazepine was discontinued, but clobazam, zonisamide, sultiame, ethosuximide, and intravenous methylprednisolone were ineffective. Adrenocorticotrophic hormone treatment markedly decreased generalized CSW, and control of ESES was maintained by sodium valproate and clonazepam.

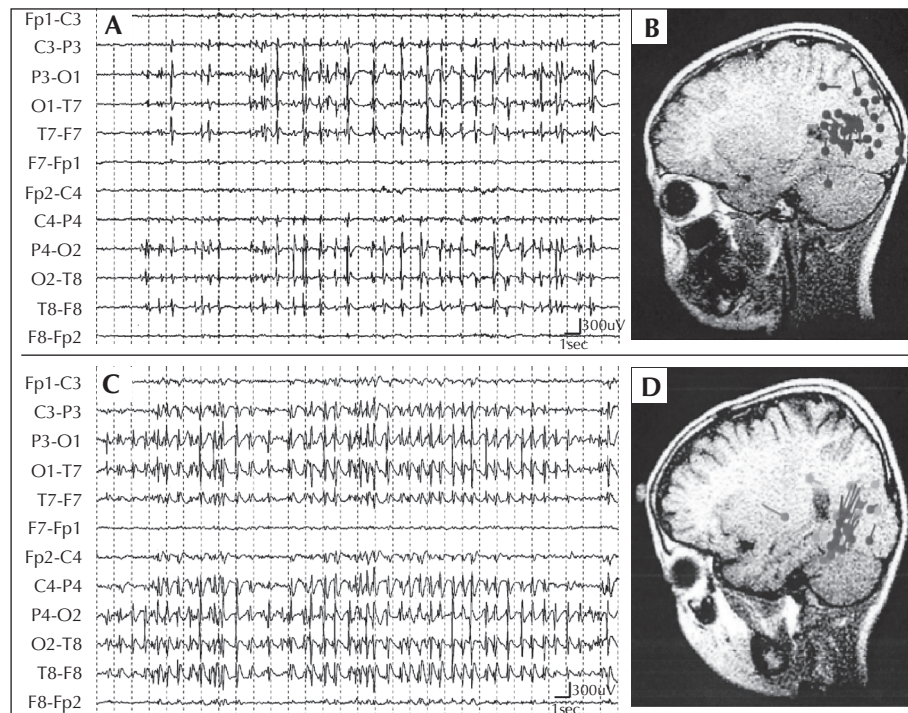


Figure 1. EEG and MEG. In Patient 1, persistent 1-2-Hz generalized spikes and waves, dominant in the occipito-temporal region, were recorded on EEG (A), and dipole clusters in and around the posterior inferior temporal cortex were recorded on MEG (B). In Patient 2, persistent 1-2-Hz generalized spikes and waves, dominant in the occipito-temporal region, were recorded on EEG (C) and dipole clusters in and around the posterior inferior temporal cortex were recorded on MEG (D).

Approximately one year was required to control ESES. At 16 years of age, EEG was normalized, and clinical seizure and epileptic discharge did not recur with sodium valproate alone.

Neuropsychological testing was performed at 11 years of age. On the Japanese WISC-III, the full, verbal, and performance IQs were 99, 106, and 90, respectively. The score for picture finding on ITPA and that for copying and delayed reproduction on ROCFT were lower than age-matched scores, showing impaired visual perception.

He passed the Japanese Kanji Aptitude Test for his age before the onset of ESES, showing excellent scores in writing Kanji. At the time of study, he had no problems in reading Kana, converting a written Kanji to Kana, and dictating in Kana after listening to a word. He also had no problems in copying, reading aloud, and identifying Kanjis. However, the correct answer rates for Kanji writing tasks for fifth- (10-year-old) and sixth- (11-year-old) grade school children were 65 and 70%, respectively. His Kanji dysgraphia consisted of morphological, phonemic, and semantic errors (figure 2). In addition to medications, the patient also underwent educational interventions in an attempt to reinforce memorization of Kanjis, such as describing out aloud how the strokes are made while writing each Kanji,

and construction of Kanjis from the radicals. Kanji dysgraphia ameliorated gradually several years after CSW was controlled, but he remained weak in his ability to write Kanji at high school.

The Osaka City General Hospital Ethics Committee approved the analysis of the patient's data and informed consent was obtained from the patients' parents for publication of clinical data.

Discussion

In Japan, learning Kanji starts in the first grade of elementary school, and children have to learn about 1,000 Kanjis during the six-year elementary school schedule. The number of Kanjis to be memorized increases with every grade, and the difficulty also increases. Both patients had no problems in writing and reading Kanji before onset of ESES. However, with the onset of occipito-temporal dominant ESES during the age at which Kanji is learnt, both patients manifested Kanji dysgraphia. Reported cases of Kanji dysgraphia involve mainly adults with cerebrovascular disorder. The responsible lesions were caused by temporal or parietal lobe injury, and many cases had concomitant reading disorder and Kana dysgraphia. The left PITC

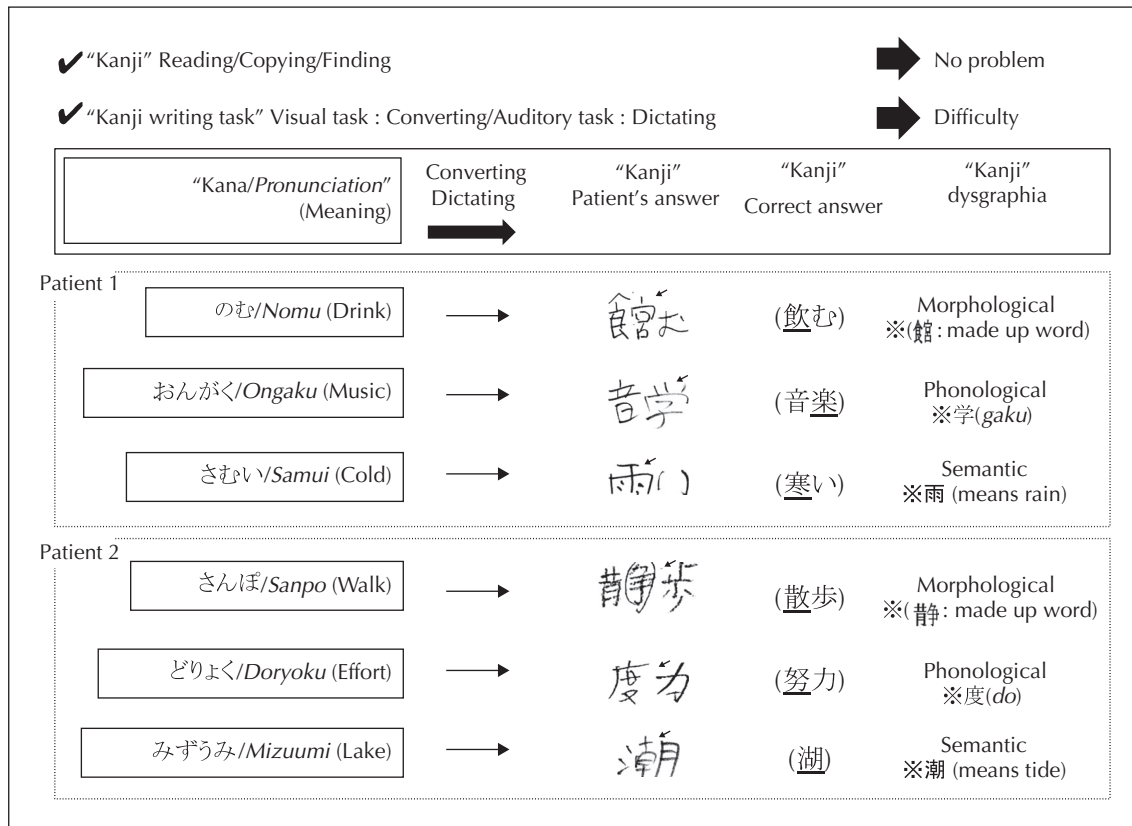


Figure 2. Schematic illustration of Kanji tasks and representative errors in writing Kanji.

In the examples given, the patients were presented with words written in Kana (first column on the left) and they wrote the Kanjis for these words (second column, handwriting). The correct Kanjis are shown in the third column, and the types of dysgraphia are explained in the fourth column.

is considered to be the lesion common to cases of pure Kanji dysgraphia without impairment of semantic understanding or reading. Acquired Kanji dysgraphia in children is very rare.

For Kanji writing, visual semantic processing, that allows letter morphology to be directly recalled, occurs in parallel with phonetic processing, that allows letter morphology to be indirectly recalled after recalling the sound corresponding to the meaning of what the subject wants to express (Uno *et al.*, 1995). In our patients, various Kanji error patterns were noted, suggesting that both phonetic and visual semantic processing to recall letters were impaired. The left PITC is an important ventral pathway of visual processing. Its cortical structure comprises columns that perceive a relatively small number of basic figures, and a limitless number of figures are perceived through their combination (Tanaka, 1996; Van Essen and Gallant, 1994). It is assumed that columns for a component of Kanji, such as the radicals, are present, and the complex morphology of Kanji can be processed by combining these columns. In addition, "Kanji storage", that combines

the meaning and phoneme, may be formed, allowing input, storage, and output of Kanji, as necessary. The left PITC may be strongly involved in the Kanji writing process. In the context of the Japanese language, acquired Kanji dysgraphia may occur due to electrical dysfunction of left PITC in patients with ESES.

LKS and CSWS are two representative encephalopathies in the ESES, sharing common underlying pathophysiology. In ESES, CSW may inhibit normal synaptic formation, resulting in local abnormalities in brain perfusion and glucose metabolism on functional neuroimaging. These abnormalities manifest as diverse cognitive dysfunctions depending on the location of the epileptic dysfunction. Auditory verbal agnosia is manifested in LKS due to functional ablation of auditory and language-related perisylvian cortex in the temporal lobe. Epilepsy and CSWS involving the frontal lobe (acquired epileptic frontal syndrome) manifests behavioural and cognitive disturbances similar to autistic regression and adult frontal syndrome (Roulet Perez *et al.*, 1993). On treatment, sodium valproate, benzodiazepines, ethosuximide,

and steroids have been proven to be effective in many previous reports as well as in the present patients. The present cases had the unique cognitive dysfunction of Kanji dysgraphia, which is distinct from that of LKS and CSWS. However, the present cases also share common features with LKS and CSWS in terms of the clinical course (the cognitive defect appeared at the time of onset of ESES), pathophysiology (electrical dysfunction resulted from CSW), neuroimaging (local abnormalities on functional neuroimaging), and response to steroids and antiepileptic drugs (sodium valproate and benzodiazepines).

Only one European case of occipito-temporal dominant CSWS has been reported in the literature, and this case had lower performance IQ than verbal IQ (Eriksson *et al.*, 2003). In our two cases, performance IQ also tended to be lower than verbal IQ, suggesting that visual processing might be impaired. The onset age of encephalopathy in both cases is rather late compared to typical LKS and CSWS. A possible reason is that the epileptic dysfunction involved a relatively localised region. Moreover, it might take time to notice Kanji dysgraphia because it is a less remarkable cognitive dysfunction compared to aphasia and behavioural problems. In the period in which ESES is evident, clinical seizure is often absent and cognitive dysfunction and behavioural problems may be the only symptom. Since both patients developed Kanji dysgraphia during their school years, during which time they learnt Kanjis with increasing complexity, their teachers misjudged their errors in Kanji writing as the result of insufficient studying. The outcome of cognitive function is usually poor in LKS and CSWS. In our two patients, treatment over relatively short periods resolved ESES, which may contribute to their recovery in competence of Kanji writing. However, the patients had onset of ESES at a critical age of Kanji writing, which may account for the long periods (several years) required for gradual amelioration of Kanji dysgraphia.

Recently, *GRIN2A* gene mutations have been associated with acquired epileptic aphasia and encephalopathies with speech and language dysfunction (Lesca *et al.*, 2013). However, no genetic studies were performed in the present cases.

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TEST YOURSELF



- (1) What is the strategy to diagnose ESES?
- (2) Which drugs are considered as first line choices for the treatment of ESES?
- (3) What will happen if epileptic dysfunction occurs in the posterior inferior temporal cortex?

Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com