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CASE REPORTS

Treatment with flunitrazepam of continuous spikes and waves during slow wave sleep (CSWS) in children

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Summary We describe our treatment of two boys with continuous spikes and waves during slow wave sleep (CSWS). One of the boys was suffering from non-convulsive status epilepticus and the other from conscious disturbance with automatism. Their ictal EEG readings showed continuous diffuse spike and wave complexes, which were considered to show electrical status. The boys were diagnosed as having CSWS, and were later diagnosed with Landau—Kleffner syndrome (LKS). EEG readings returned to normal on intravenous injection of flunitazepam (FZP) at a dose of 0.02 mg/kg, suggesting that FZP is an effective treatment for CSWS.

Introduction

Flunitrazepam (FZP) is commonly used clinically for the induction of anesthesia.[1] It has also been reported that intravenous injection of FZP relieves prolonged seizures.[2] Epilepsy with continuous spikes and waves during slow wave sleep (CSWS) is an unclassified condition[3] observed mainly in cases of refractory epilepsy. In this report, we describe our treatment of two boys with CSWS. Informed consent was obtained prior to treatment.

Case reports

Patient 1: N.K., 9-year-old male (Fig. 1)

The patient's developmental milestones were normal until he experienced non-convulsive status epilepticus at the age of 9 years and nine months.

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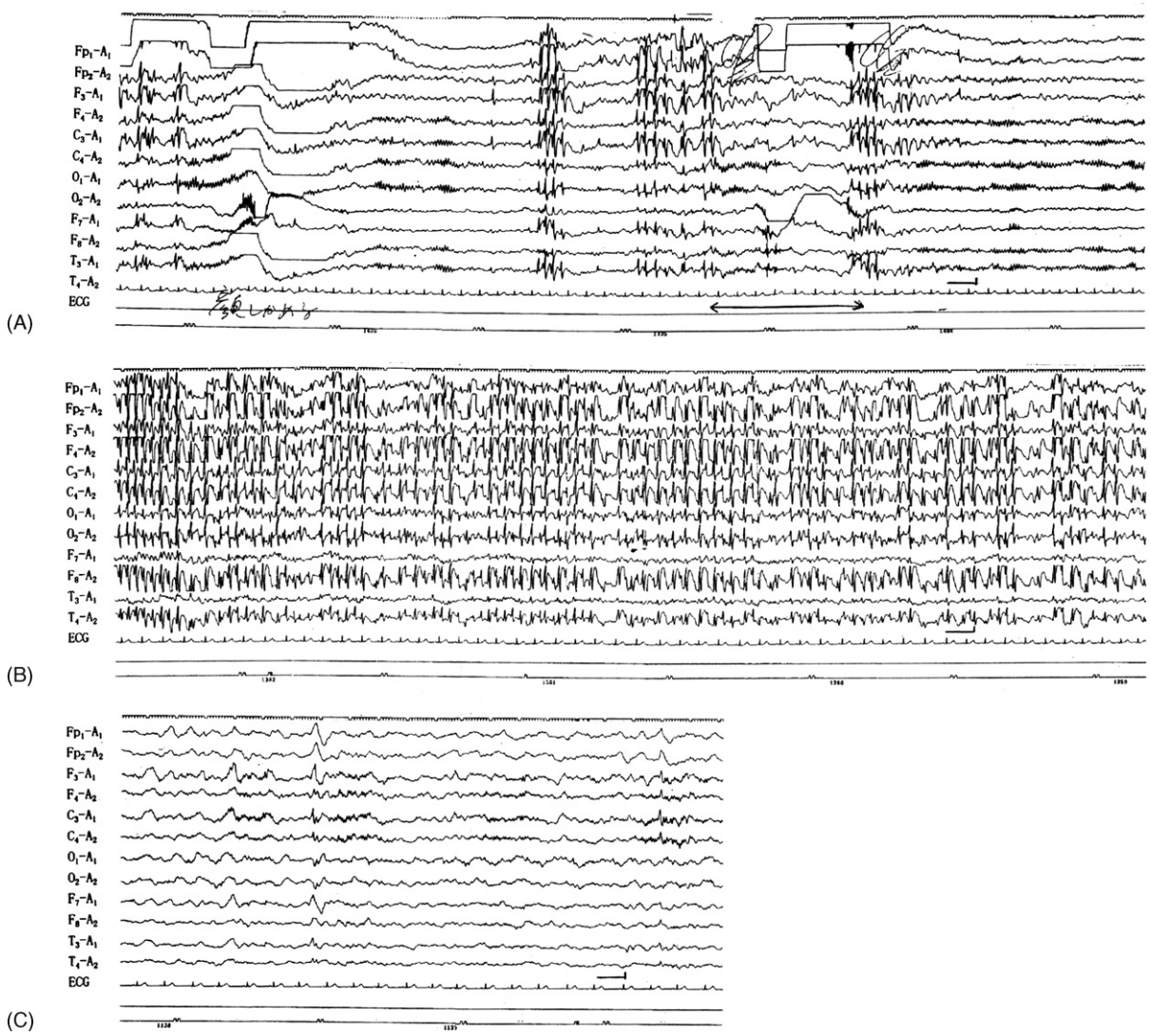

Figure 1 Nine-year-old male. (A) Waking EEG showed irregular spikes and waves. The bilateral arrow indicates the period during which his eyes were open. Paroxysmal discharges were inhibited by eye opening. (B) EEG of non-REM sleep revealed a CSWS pattern. (C) After intravenous FZP administration, epileptiform discharges disappeared. Calibration, 50 μV, 1 s.

His speech deteriorated dramatically, and his IQ score of WISC-R declined to 54. Waking EEG records showed diffuse spike and wave complexes which were attenuated by eye opening (Fig. 1A). Continuous bursts of slow spike and wave complexes occurred without any clinical symptoms during non-REM sleep (Fig. 1B). He was diagnosed as having CSWS. An intravenous injection of FZP at a dose of 0.02 mg/kg brought his EEG readings back to normal (Fig. 1C). Brain images (CT and MRI) were also normal. He was treated thereafter with oral FZP (0.002 mg/kg/day) for 2 weeks and a longer course of valpronic acid, and followed a satisfactory course including gradual recovery of his mental development. He finally graduated from elementary school and then junior high school.

Patient 2: C.K., 7-year-old male (Fig. 2)

This patient had a history of simple febrile seizures (1 year). From the age of 7 years and nine months, he suffered lost consciousness with automatism for several minutes early each morning; he also had dysarthria, sometimes spoke meaninglessly, and suffered from decreased perception. However, he was able to go to school by himself and experienced no aphasia. Sleep EEG readings recorded at our clinic revealed diffuse spike and wave complexes which were considered to show electrical status (Fig. 2A). He was

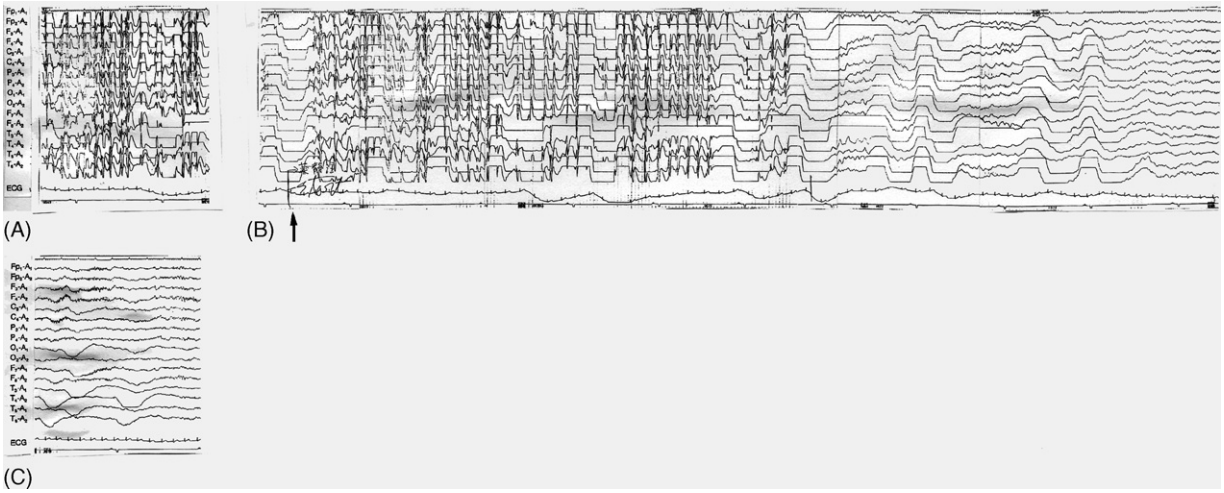

Figure 2 Seven-year-old male. (A) EEG showed diffuse irregular spikes and waves. (B) Immediately after intravenous FZP administration (arrow) epileptiform discharges disappeared. (C) Twenty minutes after FZP administration, inhibition of paroxysmal discharges was still observed. Calibration, 50 μV, 1 s.

diagnosed as having CSWS. An intravenous injection of FZP at a dose of 0.02 mg/kg returned EEG readings to normal (Fig. 2B), and they stayed in the normal range for more than 20 min (Fig. 2C). The patient woke up 30 min after the injection, and his responses to subsequent questions were appropriate. His brain images (CT, MRI and SPECT) were normal. He was treated thereafter in the same way as Patient 1. He regained smooth speech patterns and completed elementary school satisfactorily.

Discussion

Epilepsy with CSWS is defined by Tassinari et al.[4] and epileptic seizures with CSWS are thought to be intractable even with polytherapy involving antieleptic drugs.[5] Several reports had documented the potent anticonvulsive effects of FZP in animals[6] and humans,[2,7] so we decided to try it on two patients with CSWS. We were able to demonstrate its efficacy in inhibiting electrical status on EEG. Long-term use of FZP is likely to result in side effects (intolerance, drowsiness, etc), but it seems to be a good reliever of ictal states with CSWS. It has been reported that some patients with CSWS can be regarded as Landau—Kleffner syndrome (LKS) sufferers.[8,9] Indeed, it is suspected that CSWS syndrome and LKS may well be two sides of the same coin.[5] Because of their satisfactory long-term outcomes, we diagnosed the two present cases as having LKS.[5] Although no previous reports have indicated the use of FZP for CSWS, we suggest from our experience with the two cases described here that it may be a beneficial treatment.

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References

1. Van de Walle J, Lauwers P, Adriaensen H. Clinical experimentation with flunitrazepam (Ro 05-4200). *Acta Anaesthesiol Belg* 1974;**25**:350—8.
2. Sumi K, Nagaura T, Sakata N, Nishigaki T, Akagi M. Intravenous flunitrazepam for status epileptics. *Acta Paediatrica Japonica* 1989;**31**:563—6.
3. Protocol for revised classification of epilepsies and epileptic syndromes. Commission on Classification Terminology of the International League Against Epilepsy. *Epilepsia* 1989;**30**: 389—99.
[4] Tassinari CA, Bureau M, Dravet C, Rojer J, Daniele-Natale O. Electrical status epilepticus during sleep in children (ESES). In: Stermann MB, Shouse MN, Passouant P, editors. *Sleep and epilepsy*. London and New York: Academic Press; 1982 . p. 465—79.
[5] Morikawa T, Seino T, Watanabe M. Long-term outcome of CSWS syndrome. In: Beaumanoir A, Bureau M, Deoona T, Mira L, Tassinari CA, editors. *Continuous spikes and waves during slow sleep*. London: John Libbey & Company Ltd.; 1995 p. 27—36.
6. Kanaya J. Effect of benzodiazepine derivatives on secondary propagation of convulsive seizures. *Tenkan Kenkyu* 1985;**3**: 164—73. (in Japanese).
7. Ono J, Mimaki T, Tagawa T, Tanaka J. Intravenous injection of flunitrazepam for status epileptics in children. Two case reports. *Brain Dev* 1988;**10**:329—32.
8. Landau WM, Kleffner FR. Syndrome of acquired aphasia with convulsive disorder in children. *Neurology* 1957;**7**:523—30.
9. Hirsch E, Marescaux C, Maquet P, Metz-Lutz MN, Kiesmann M, Salmon E, et al. Landau—Kleffner syndrome: a clinical and EEG study of five cases. *Epilepsia* 1990;**31**:756—67.