ELSEVIER

Reversible Altered Consciousness With Brain Atrophy Caused by Valproic Acid

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A 5-year-old female developed alteration of consciousness during 3 days of long-term treatment with valproic acid for localization-related epilepsy. Computed tomography revealed cerebral atrophy, and electroencephalography presented slow background activity. Consciousness cleared only 12 hours after valproic acid was discontinued, and normal electroencephalography results were evident 1 week later. Cerebral atrophy was nonexistent 2 months later. This rapidly developing but reversible alteration of consciousness in parallel with brain atrophy is recognized as a rare idiosyncratic adverse effect of valproic acid.

Yamanouchi H, Oka T, Imataka G, Nakagawa E, Eguchi M. Reversible altered consciousness with brain atrophy caused by valproic acid. Pediatr Neurol 2003;28:382-384.

Introduction

Stupor or coma induced by valproic acid may be associated with hyperammonemia with or without hepatic dysfunction [1,2]. Different from this category, reversible cognitive and behavioral deterioration associated with a radiologic finding of brain atrophy has been reported as a rare adverse effect of valproic acid and is characterized by a subacute or chronic course without hyperammonemia [3-5]. Recovery occurs throughout weeks or months after discontinuation of valproic acid therapy. Reported here is valproic acid–related alteration of consciousness associated with brain atrophy that progressed throughout only 3 days and resolved within 12 hours after discontinuation of valproic acid.

Case Report

This 5-year-old female was the product of a 39-week gestation and a normal delivery. She manifested normal developmental milestones. She remained healthy until aged 2 years, when she presented with drop episodes followed by unconsciousness for several minutes. Electroencephalogram (EEG) demonstrated normal background activity during the wakeful state and bilateral intermittent focal spikes throughout anterior temporal and central regions during sleep recording. She was diagnosed with localization-related epilepsy. Valproic acid was introduced at 10 mg/kg/day and maintained at 15 mg/kg/day. Blood-screening tests, including liver function tests, blood cell counts, and serum amylase assays, performed at 2 weeks and 2 months after valproic acid introduction, revealed normal findings. No seizures were observed at the above dose of valproic acid until the patient was 5 years of age, when a brief generalized clonic seizure occurred. Computed tomography (CT) disclosed normal findings (Fig 1A, B). Because the recurrent seizure was associated with a low serum concentration of valproic acid (25.7 μg/mL), the valproic acid dose was increased to 20 mg/kg/day, with a resulting steady-state serum concentration of 76.4 μg/mL.

After 3 months, she was admitted to the hospital because of alteration of consciousness, which developed throughout 3 days. Before this disturbance, mental and motor development had been normal, even after seizure onset. She could maintain arousal and was reactive to painful or tactile stimuli but had difficulty stating her name. She demonstrated little interest in her surroundings and hardly talked with her mother. She was not incontinent, agitated, or irritable. Physical and neurologic examination results were normal. Routine complete blood cell count was normal, as were levels of serum electrolytes, glucose, calcium, phosphate, urea nitrogen, creatinine, ammonia, lactate, and pyruvate; liver-function test results were normal, and carnitine, amino acid, and organic acid analysis yielded normal results. The serum valproic acid concentration was 107 μg/mL. CT indicated mild enlargement of cerebral sulci and pericerebral spaces; ventricular size was normal and no cerebellar or brainstem atrophy was observed (Fig 1C, D). EEG during wakefulness revealed diffuse slowing of background activity (Fig 2); a sleep recording depicted normal background activity.

Valproic acid treatment was discontinued on admission because of previous case reports linking it to reversible mental deterioration associated with brain atrophy [3-5]. The next morning, approximately 12 hours after admission, her consciousness level became completely normal. EEG repeated 1 week after valproic acid discontinuation manifested normal background activity during wakefulness, and no paroxysmal discharge was observed (Fig 3). Administration of phenobarbital was begun 10 days after the discontinuation of valproic acid. Serial CT

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Received July 25, 2002; accepted December 10, 2002.

doi:10.1016/S0887-8994(03)00005-5 • 0887-8994/03/$—see front matter

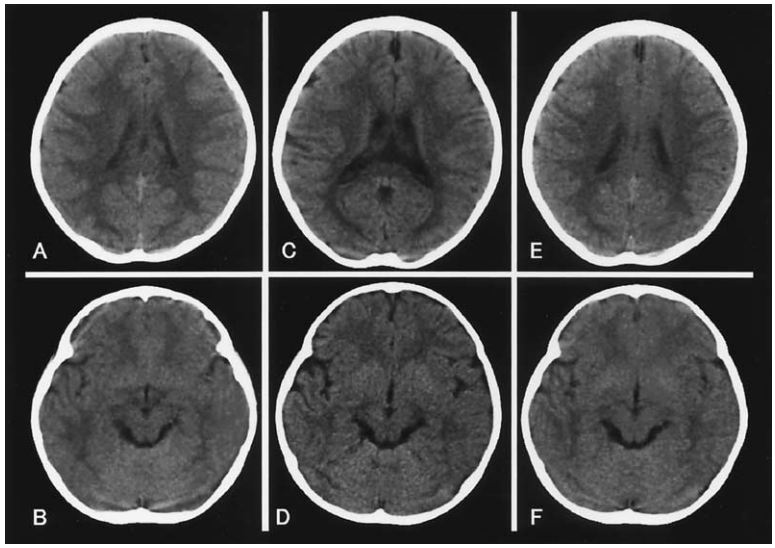

Figure 1. Serial brain CT. (A, B) Two years before alteration in consciousness. (C, D) On admission. (E, F) Two months after discontinuation of valproic acid. Observe normal findings in A and B, as well as E and F, contrasting with mild atrophic changes in the cerebrum in C and D.

demonstrated improvement in the atrophic change of the cerebrum 1 month later, followed by a complete return to normal after 2 months (Fig 1E, F). Subsequent magnetic resonance imaging revealed no significant change in the brain. On follow-up in the outpatient department 5 months after discontinuation of valproic acid, she manifested no abnormalities, and her parents described her behavior and mental function as entirely normal.

Discussion

Rapidly developing alteration of consciousness associated with brain atrophy and its dramatic resolution after discontinuation of valproic acid treatment characterizes the clinical feature in this patient. EEG in the wakeful state revealed slowing background activity when the patient manifested altered consciousness, and EEG activity returned to normal when she recovered consciousness. Rapid depression of consciousness raises suspicion of valproic acid–related encephalopathy with hyperammonemia, which may occur in isolation [2] or in association with such underlying disorders as urea cycle enzyme deficiency [1]. Mitochondrial disorders such as MELAS (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes) [6] and cytochrome c deficiency with hepatic failure [7] can be triggered by valproic acid. Carnitine deficiency may predispose patients to encephalopathy upon initiation of valproic acid therapy [8]. Finally, paradoxic epileptogenic effects of valproic acid, particularly induction of nonepileptic-status epilepticus, also are part of the differential diagnosis [9].

This patient's clinical features and course were similar to those in previously reported pediatric cases [3-5] in which valproic acid was associated with reversible cognitive or behavioral deterioration and brain atrophy. Such states often persist for months, with reduction or disappearance of mental deterioration requiring weeks ([3]; patient 1 in [4]; [5]) or even months (patient 2 in [4]). Compared with those described in these reports, this patient appears to be unique in that clinical manifestations developed throughout only 3 days and disappeared only 12

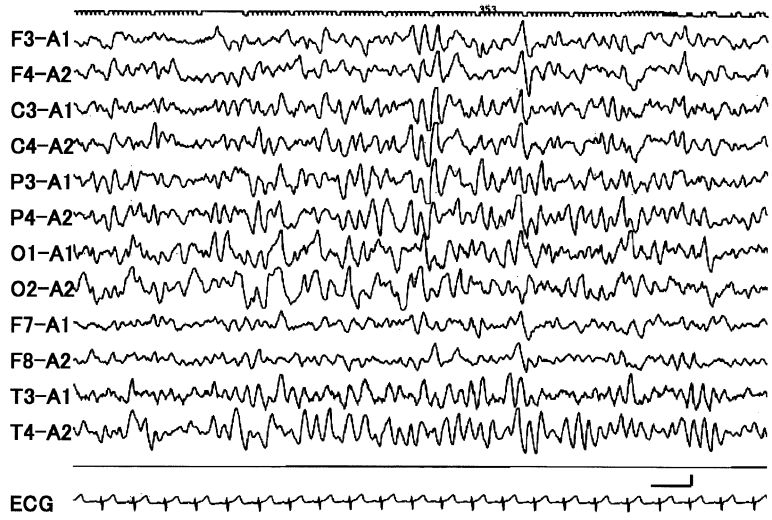

Figure 2. Waking electroencephalography on admission, revealing diffuse slowing of background activity. Calibration marks: 1 second, 100 μV.

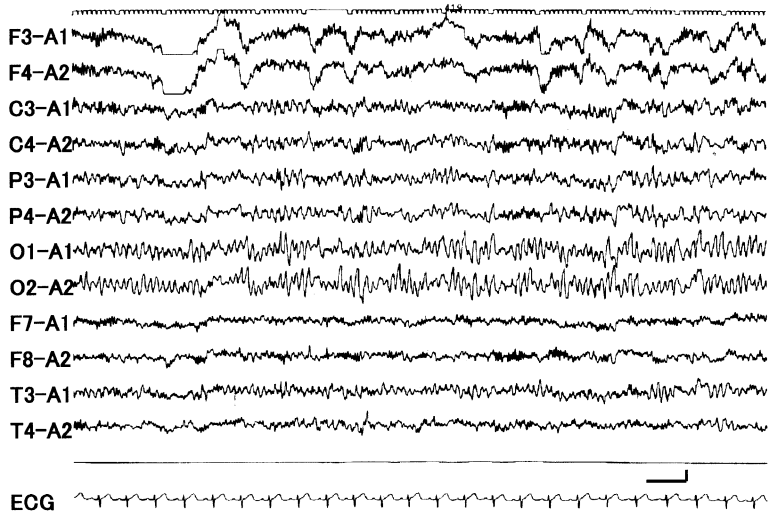

Figure 3. Waking electroencephalography 1 week after discontinuation of valproic acid, revealing normal background activity. Calibration marks: 1 second, 100 μV.

hours after valproic acid discontinuation. The abnormalities observed were not mental deterioration, as in previous reports [3-5], but instead appeared to be a rapidly progressive alteration in state of consciousness. Had valproic acid treatment been continued, this patient might have appeared to manifest mental deterioration or dementia, possibly raising suspicion of a neurodegenerative disorder with a subacute or chronic course.

An important feature in this patient is the correlation between clinical manifestations and EEG findings of slowing during wakefulness. Most previously reported pediatric cases of reversible brain atrophy and mental deterioration associated with valproic acid therapy demonstrated normal background EEG activity [4,5]. However, McLachlan's study [3] indicated that the waking EEG during a mentally abnormal state of a patient receiving valproic acid treatment presented slowing of background activity (8-Hz slow alpha rhythm) dominated in the bilateral occipital area in a patient 13 years of age.

Valproic acid–induced mental changes and brain atrophy may be associated with parkinsonism in adults [10]. Armon et al. reported that 11 of 16 patients manifesting parkinsonism during valproic acid therapy demonstrated progression of cerebral atrophy [10]. CT was obtained in two patients whose signs were reversible after discontinuation of valproic acid. In pediatric cases, mental change and brain atrophy can occur either in isolation ([5] and present case) or in association with neurologic signs such as tremor, ataxia, and nystagmus [3,4]. Thus, this syndrome is variable: mental state may deteriorate rapidly, subacutely, or chronically, and with or without other neurologic signs, such as tremor. Rate of recovery also is variable.

The pathogenesis of these reversible phenomena is unknown, although interference with the pituitary-adrenal axis and changes in blood-brain barrier permeability have been hypothesized [3]. Irrespective of mechanisms, a drug effect should be considered whenever brain atrophy and rapid change of consciousness occur in a patient receiving valproic acid. Even if other indications of valproic acid toxicity are lacking, valproic acid treatment should be discontinued without delay as further evaluation proceeds.

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