Lethal Obesity Associated with Sodium Valproate in a Brain-Injured Patient

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Abstract: A 34-year-old man developed posttraumatic epilepsy and a disinhibited orbitofrontal syndrome following severe head trauma at age 22. After an 11-year prison term marked by repeated impulsive aggression, he was transferred to a state psychiatric hospital. Replacement of phenytoin by valproic acid resulted in a 100-lb weight gain, exacerbation of sleep apnea, and right heart failure. Despite replacement of valproate with topiramate, he died of a cardiorespiratory arrest during a seizure. This case illustrates the potential risks associated with valproate therapy in the obese brain-damaged population.

Key Words: appetite, orbitofrontal, valproate

(*Cog Behav Neurol* 2005;18:98–101)

Sodium valproate (VPA) is a broad-spectrum anticonvulsant indicated for partial and generalized seizures. It is also commonly used for stabilization of endogenous and acquired mood and behavioral disorders.[1–3] One of the limitations to its use has been weight gain, with its associated morbidity. We present a patient who developed lethal weight gain following the introduction of VPA after a traumatic brain injury.

CASE PRESENTATION

RP was a 34-year-old right-handed man transferred to a state psychiatric hospital from prison for violent sexual assault on an elderly woman.

Development and Psychosocial History

RP was the product of a middle-class family. Adjustment and scholastic problems were evident in primary school. After dropping out of high school at age 17, he abused alcohol and experimented with marijuana and cocaine. He had numerous contacts with the police, beginning in adolescence, for verbal threats, possession of knives, trespassing, and retail theft. He never maintained steady employment. His personality was described as immature, dependent, egocentric, and impulsive. He was a loner, subject to violent temper outbursts. Parole violation and other antisocial behaviors (eg, burning a church) along with behavioral regression and social deterioration led to psychiatric hospitalization at age 20. Full-Scale IQ was 75 on the Wechsler Adult Intelligence Scale–Revised (WAIS-R), Verbal IQ was 77, and Performance IQ was 74, without significant scatter on subtests.[4] He carried diagnoses of antisocial personality disorder, borderline mental retardation, and prepsychotic schizophrenia treated with quetiapine 800 mg/day.

At age 22, RP jumped in front of a car in a failed suicide attempt. He sustained a massive left subdural and small right epidural hematomas requiring neurosurgical evacuation. Three weeks post injury, he was mute and incontinent, unable to follow verbal directions or imitate simple hand gestures. There were signs of frontal and perceptual impairment: He closed a stimulus figure instead of copying it and was unable to trace a simple maze. The occupational therapist noted that he tried "to put everything in his mouth." Behavior worsened following this injury, with the appearance of perseverative, concrete, illogical, and tangential thinking with delusional and grandiose content and poor insight and judgment. Nine months post injury, WAIS-R Full-Scale IQ was 68, Verbal IQ was 69, and Performance IQ was 70. Compared with previous testing, there were significant declines in attention, concentration, and short-term memory. Forward Digit Span was 8 in 1987 and 5 in 1988; Reverse Digit sspan was 4 in 1987 and 3–4 in 1988. The Benton Visual Retention Test[5] suggested acquired cognitive impairment.

At age 23, RP was convicted of aggravated sexual assault on an elderly woman, including vaginal penetration with a broomstick and threats to kill. During an 11-year prison term, he caused >100 incidents of disorderly behavior and violation of rules. He showed delusional misidentification of his ex-wife and female prison guards. Sporadic generalized seizures were treated with phenytoin. An electroencephalogram (EEG) at age 23 showed disorganization and slowing in the anterior regions without epileptiform changes.

At age 34, RP was transferred to a psychiatric hospital for assessment of his competency to return to the community. He was obese (256 lbs), with long, unkempt hair and beard and multiple tattoos. Behavior was boisterous, disruptive, and intimidating to staff and other patients. He was verbally and occasionally physically assaultive. He made frequent references to his genitalia and sexual innuendos to female staff and was found dancing naked in his room. He salted his food excessively and snatched food from other patients' trays. He insisted that he was competent to live in the community. He was markedly concrete on proverbs.

Course in Hospital

Phenytoin was replaced with VPA for his seizure disorder and for behavioral stabilization.[1,3] RP was noted to nap frequently during the day and to snore loudly at night. Daytime drowsiness worsened as the dose of VPA was gradually increased to 750 mg bid (serum level 94 μg/mL; therapeutic range 50–125 μg/mL). Although a formal

Received for publication December 12, 2003; revised May 20, 2004; accepted November 19, 2004.

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sleep study confirmed obstructive sleep apnea syndrome, he refused to wear a continuous positive airway pressure (CPAP) mask.

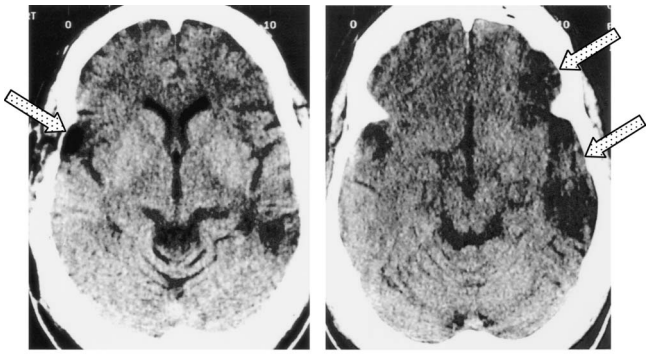
Over the following 9 months, while on VPA, RP's weight increased from 256 to 361 lbs. He developed scrotal edema and marked ankle swelling, which were treated with Aldactone. He was lethargic with tachycardia on minimal exertion. He had a "dizzy spell," which he recognized as a seizure aura. EEG showed an active polyspike-wave disturbance in both fronto-central-temporal regions, more marked on the left. Brain computed tomography scan showed extensive encephalomalacia involving the left inferior frontal convexity and inferior temporal lobe, extending superiorly into the left midtemporal cortex and inferior parietal lobe (Fig. 1). The right temporal pole was atrophic. VPA was tapered over 3 months, and topiramate was begun (Fig. 2).

Despite stepwise increases of topiramate to a maximum dose of 400 mg bid, "terrifying and horrifying" seizure auras with a "rotten" feeling continued. His weight fluctuated between 318 and 335 lbs. A cardiologist diagnosed right heart failure. Two generalized seizures occurred during abrupt lowering of serum topiramate levels by massive diuresis complicated by hypokalemia (2.5 mEq/L; normal 3.5–5.0 mEq/L).[6] Seven months after beginning topiramate, at a dose of 400 mg bid, he had a spontaneous generalized seizure lasting 7 minutes. Levetiracetam was started.

He became increasingly lethargic. Cellulitis of his edematous right leg was treated with intravenous cefazolin. Another "horrible" seizure aura occurred while he was receiving levetiracetam 1500 bid and topiramate 400 bid. Several weeks prior to his death, he had begun wearing the CPAP mask most of the night, which seemed to reduce his daytime sleepiness. At 6:30 AM, he was observed to be having a generalized seizure in his sleep while wearing the CPAP mask. He was found in asystole and could not be resuscitated.

Autopsy

The lungs were slightly congested and edematous; the heart, aorta, and pulmonary artery and veins were normal to gross and microscopic examination. The brain showed multifocal areas of encephalomalacia involving both inferior frontal lobes and orbitofrontal (OF) surfaces and the inferior left temporal lobe. Microscopically, marked tissue loss and gliosis were seen in these areas. The hippocampi were intact. The left amygdala contained normal-appearing neurons in adequate numbers. There was a focus of white matter rarefaction and gliosis in the uncinate fasciculus in the left inferior frontal lobe, contiguous with the white matter adjacent to the amygdala. Unfortunately, microscopic sections were unavailable from the right amygdala.



A. B.

FIGURE 1. Brain computed tomography scan of patient RP, showing atrophy of the right temporal pole (A) and extensive encephalomalacia in the left inferior frontal and temporal areas (B) (arrows).

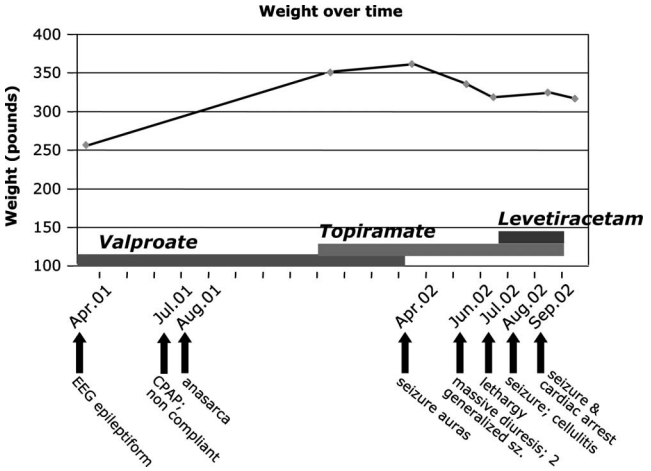


FIGURE 2. Time sequence of weight gain, pharmacotherapy, and clinical course for patient RP. EEG, electroencephalogram; CPAP, continuous positive airway pressure; sz, seizure.

DISCUSSION

RP developed a disinhibited behavioral syndrome superimposed on a premorbid antisocial personality disorder following traumatic brain injury. Pathology examination showed bilateral OF damage and disruption of the left uncinate fasciculus linking the OF cortex and the amygdala. After the introduction of VPA, drowsiness and a voracious appetite developed.

Damage to medial temporal and basal frontal structures disrupts learned associations between food and appropriate behavior. Bilateral damage to the anterior temporal lobes, including the amygdalae, results in the Klüver–Bucy syndrome, characterized by indiscriminate and inappropriate sexual activity, placidity, and "hypermetamorphosis," or compulsive oral exploration of the environment.[7,8] The common denominator is a mismatch between a drive (hunger) and the appropriate extrapersonal target.[9]

Despite radiologic signs of bitemporal injury, our patient did not display the full clinical features of the Klüver–Bucy syndrome. His euphoria, irritability, social and sexual impropriety, impaired judgment, impulsiveness, indifference to risks and rules, inability to defer reward, and pathologic oral behavior instead suggested dysfunction of the OF cortex.[10–12]

Together with the amygdalae, the OF cortex forms part of a widespread network of limbic and sensorimotor structures involved in the evaluation and control of goal-directed behavior, including the regulation of appetite.[13] Presentation of food to hungry subjects activates limbic structures involved in motivation, attention, and behavioral control, including the amygdala and hippocampus, insula, ventromedial and prefrontal cortex, and anterior cingulate.[14] Amygdala activation occurs at a relatively early stage of appetitive behavior, reflecting its role in evaluating the adaptive value of potentially rewarding stimuli.[15] OF activation, in contrast, reflects the hunger or satiety state of the subject.[14,16,17] Afferents from

visual, olfactory, and primary taste cortex in the anterior insula converge on OF neurons, which also have dense reciprocal connections with the amygdalae. Different populations of OF neurons have highly specific responses to gustatory, olfactory, auditory, and visual stimuli; other subpopulations respond specifically to multimodal inputs.[16] The amygdalae and OF cortex thus participate in the adaptive and flexible regulation of eating in response to the changing value of a food reward.[17]

The pathologic oral behavior of RP resembled that of hyperphagic patients with frontotemporal dementia, in whom the responsible lesion likely involves the OF cortex.[18,19] RP's hyperphagia, which was evident in the weeks following his traumatic brain injury, took the form of excessive salting of his food and theft of food. Pathologic eating worsened after VPA was started, leading to morbid obesity, which ultimately contributed to his death.

Weight gain associated with VPA has been reported since shortly before its release as an antiepileptic agent in 1983[20,21] and after its release, with reports of weight gain in both adults[22–26] and children.[27] Weight gain of 8–14 kg occurs in 20% of cases, although estimates of weight gain vary from 8% to 59% of cases in different studies.[28,29]

The mechanism of weight gain with VPA is not clear. Increased food intake as well as decreased energy expenditure have been reported.[29] Altered thermogenesis and greater availability of long-chain fatty acids as a result of competitive binding to serum proteins have also been postulated.[29] VPA has been linked to hyperinsulinemia and to low serum concentrations of insulin-like growth factor binding protein-1.[26,30] An increased incidence of polycystic ovary syndrome in women treated with VPA[26,30] has been debated.[31] A decrease in carnitine levels does not appear to be explanatory.[32] There are some reports of increased serum leptin in obese patients treated with VPA,[33] but other reports suggest no evidence of an independent role for leptin.[34]

We think that VPA triggered massive weight gain in our patient with an underlying traumatic lesion of the OF-amygdala network, which disrupted appetite regulation. The amount of weight gain is difficult to assess, as some of the weight was due to edema caused by right heart failure. We suggest that the introduction of VPA in RP set in motion a cycle of morbidity that ultimately proved fatal: Obesity led to exacerbation of sleep apnea syndrome. Repeated hypoxemia led to pulmonary hypertension, with eventual decompensation of right heart failure.[35] Repeated hypoxemia may have lowered seizure threshold and contributed to poor seizure control. The severe hypoxemia that accompanies a generalized seizure may have contributed to his terminal cardiac arrest. Alternatively, bradycardia or a malignant tachyarrhythmia, common in patients with sleep apnea syndrome,[36,37] may have triggered the terminal seizure.

CONCLUSION

We advise caution to clinicians who contemplate using VPA for the treatment of epilepsy and for behavioral stabilization in the brain-damaged population, especially if there is concomitant obesity, sleep apnea syndrome, or an eating disorder.

ACKNOWLEDGMENTS

The authors thank Dr. Steven Shapiro (Medical Examiner for the State of Vermont) and Dr. William Pendlebury (Department of Neuropathology, University of Vermont) for contributing the autopsy findings. We also thank the anonymous reviewers of this manuscript for their helpful comments.

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