Valproic Acid-Associated Neurologic Syndrome in Chronic Mental Illness: A Case Report

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Introduction

A forty-eight year old, divorced, white female with a reported seventeen-year history of chronic undifferentiated schizophrenia had been hospitalized for many years on various units in our hospital. The patient's symptomatology for the preceding ten years was marked by paranoid beliefs and frequent episodes of screaming and attacking staff without warning. She had been tried on multiple pharmacologic treatment strategies involving neuroleptics, with valproic acid added for much of the interval. There had been a number of attempts to discharge the patient, none lasting more than several months. Upon transfer to the current hospital unit in 2005, the patient appeared to be responding to internal stimuli, reported delusions concerning conspiracies against her family and that the staff had killed her family. The accusations were often expressed with high-volume screaming, which had become a salient component of the unit's ambience. The patient was perceived as being chronically "out-of-control."

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Observational Methods

Over a period of several years preceding transfer to the current unit, the patient had also demonstrated evidence of a progressive, but fluctuating dementia-like process. Her hospital course was noted to include periods of cognitive decline marked by an inability to recall the names of staff with whom she had constant interactions, a lack of orientation to time, place and person, an inability to be reoriented despite constant reminders, and an unsteady gait. She also suffered from cataracts. The patient sustained a hip fracture from a fall shortly after transfer to the unit. Also, upon transfer to the unit, her regimen had been largely unchanged for several years, including Depakene (1750 mg/day; valproate level = 83.6 ug/ml taken shortly after transfer), haloperidol concentrate recently increased (upon transfer due to severe paranoia) to 3 mg four times a day from three times daily, clonazepam 2 mg twice a day (increased upon transfer from 1 mg po bid due to severe anxiety), Risperdal Consta 50 mg IM every 2 weeks, and benztropine 1 mg twice a day. In an attempt to reduce the persistent affective and behavioral instability and paranoia, quetiapine was initiated at 25 mg daily. Repeat assessments for side effects reflected in the psychiatric progress notes revealed no evidence for extrapyramidal symptoms-parkinsonism side effects. A trial of diphenhydramine 25 mg twice a day in place of benztropine was attempted with a similar goal, but resulted in immediate dramatic sedation, rapidly reversed with diphenhydramine discontinuation (within several hours). Benztropine was resumed. Several months later, for treatment of a cough associated with an upper respiratory infection, Robitussin DM was initiated. This resulted in lethargy, comparable to that

previously found when diphenhydramine had been added. Sensorium examinations on mental status exam testing as reflected in the monthly psychiatric progress notes revealed a sharp decline in cognitive functioning as evidenced by impairment in all domains of memory and orientation. Nursing notes revealed a patient spiraling down into total care that included assistance with toileting, eating, transitioning positions from wheelchair to standing to bed, daily grooming and basic hygiene. The lethargy became sufficiently pronounced during the ensuing week that all oral psychotropic medications were held, including haloperidol, quetiapine, clonazepam, and Depakene (the Robitussin regimen having been completed).

While numerous factors may account for the development of a dementia-like state in this patient, valproic acid has become increasingly recognized as an agent associated with long-term cognitive and neurologic compromise.

Results

MRI without contrast revealed prominence of ventricles and sulci bilaterally that was considered appropriate for the patient's age, no sign of acute infarct and normal gray/white matter differentiation. There was no mass effect or midline shift and no evidence of hydrocephalus. Benztropine and Risperdal Consta were continued. During the following week, the patient returned to a markedly more alert state. In addition, she demonstrated dramatic improvement in the chronic cognitive symptoms, awareness and recall of many events in her immediate surroundings, a steady gait and many fewer outbursts. She was now often pleasant upon approach and, while showing moderate irritable mood, smiled at times. During the following two weeks, some of the patient's symptoms returned including insomnia and paranoid ideation. Affective instability, agitation and rage attacks were present intermittently. Clonazepam was restarted at the previous dose, quetiapine was resumed (well tolerated and titrated to 125 mg/three times a day) and haloperidol was provided on an as needed basis (2-3 doses, weekly of 5 mg). The only agent not restarted was valproic acid (and the patient did not receive additional diphenhydramine or Robitussin). After several weeks on this regimen, the patient continued to show a clear sensorium with full orientation, only mildly impaired memory and concentration, and a strong and steady gait. Delusions and hallucinations and angry outbursts persisted. The patient, who had frequently required 1:1 observation, progressed behaviorally so as to earn privileges such as supervised trips off the hospital grounds.

Discussion/Conclusions

This case demonstrates several clinical issues that may be all too common in the care of chronic hospitalized patients with psychotic disorders manifesting disruptive and threatening behaviors that do not appear to respond to pharmacotherapy. The approach to such patients, who can be frustrating and frightening for staff, not infrequently results in polypharmacy, with medications added in an attempt to control "treatment-resistant" behavior. Patients showing persistence, if not exacerbation, of symptoms are often continued on existing polypharmacy as still more agents are added. In extended care settings, polypharmacy may be maintained when patients are transferred to different units, without the new staff having had direct experience with the evolution of the medication regimen.

While numerous factors may account for the development of a dementia-like state in this patient, valproic acid has become increasingly recognized as an agent associated with long-term cognitive and neurologic compromise. Cases of reversible neurotoxicity with long-term valproic acid treatment have been reported, both with and without evidence of hepatic toxicity. These can present as a neurodegenerative condition affecting multiple systems, often with parkinsonism and cognitive impairment (1-4). Such syndromes may be more likely to develop in patients treated with polypharmacy and in those with concurrent medical disorders (2, 4, 5). The rapid and dramatic sedating effects of added sedating agents such as diphenhydramine or dextromethorphan with guaifenesin in the current patient may reflect exacerbation of an encephalopathic state associated with valproate. While the patient has not been rechallenged with these sedating agents, it is of note that the current regimen included restoration of all other psychotropic agents, in whole or part, and higher dose quetiapine, which is often sedating, without inducing a return of the lethargy or cognitive compromise.

Further, a review of the patient's chart going back more than a decade revealed a similar phenomenon in the course of extended use of valproic acid since at least 1998. Following an incident of lethargy in late 2004, when the patient contracted pneumonia, psychotropic medications were also discontinued briefly, with valproate not restarted for approximately six months. During that interval, the patient also showed improved alertness, cognition and ambulation, which gradually declined toward the more recent state following resumption of valproate. While the course of the patient's illness suggests that valproate was a key element in inducing her neurologic syndrome it should be noted that the patient's haloperidol and clonazepam had been increased before the onset of that syndrome. This had not occurred in earlier episodes. It cannot be ruled out, however, that the aggregate effects of the potentially sedating medications

contributed to the syndrome. The higher dose haloperidol, which was not fully restored subsequently, may have interacted with the valproic acid to increase vulnerability.

Education of staff and families concerning the multiple pathways to behavioral stability is an important and challenging goal in effective patient care.

While the risks associated with polypharmacy have been emphasized (6-7), the challenges of working with patients who demonstrate persistent behavioral dyscontrol and threatening behavior may counterbalance reservations about such practices. Staff who consider themselves and other patients at risk are often reluctant to remove agents considered to be "tried and true." Staff tend to respond to persistent "in-your-face" behaviors with calls for more medication, assuming that more is better. Staff may also tend to become fatalistic about patients who present with prominent and apparently progressive "organic" features. Even improved clinical state may be viewed as suspect, with staff advocating resumption of medications to prevent deterioration. An effective working relationship within the treatment team, therefore, was important to maintaining reduced pharmacotherapy in this patient. Education of staff and families concerning the multiple pathways to behavioral stability is an important and challenging goal in effective patient care.

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References

1. Armon C, Shin C, Miller P, Carwile S, Brown E, Edinger JD, et al. Reversible parkinsonism and cognitive impairment with chronic valproate use. Neurology 1996;47(3):626-635.

2. Hommet C, Mondon K, de Toffol B, Constans T. Reversible cognitive and neurological symptoms during valproic acid therapy. J Am Geriatr Soc 2007;55(4):628.

3. Mayerhoff DI, Nurenberg J, Shah S, Schleifer SJ. Neurotoxicity associated with free valproic acid. Am J Psychiatry 2005;162(4):810.

4. Ristic AJ, Vojvodic N, Jankovic S, Sindelic A, Sokic D. The frequency of reversible parkinsonism and cognitive decline associated with valproate treatment: a study of 364 patients with different types of epilepsy. Epilepsia 2006;47(12):2183-2185.

5. Cysique LA, Maruff P, Brew BJ. Valproic acid is associated with cognitive decline in HIV-infected individuals: a clinical observational study. BMC Neurol 2006;6:42.

6. Centorrino F, Goren JL, Hennen J, Salvatore P, Kelleher JP, Baldessarini RJ. Multiple versus single antipsychotic agents for hospitalized psychiatric patients: case-control study of risks versus benefits. Am J Psychiatry 2004;161(4):700-706.

7. Patrick V, Schleifer SJ, Nurenberg JR, Gill KJ. Best practices: An initiative to curtail the use of antipsychotic polypharmacy in a state psychiatric hospital. Psychiatr Serv 2006;57(1):21-23.