Reversible valproic acid-induced parkinsonism and cognitive impairment in an elderly patient with Bipolar Disorder I

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SUMMARY

Valproic acid (VPA) is approved by the Food and Drug Administration (FDA) for the treatment of manic or mixed episodes associated with bipolar disorder. VPA is also used off-label to treat other conditions in psychiatry such as impulse control disorders, major depression, and posttraumatic stress disorder (PTSD). Although VPA is mostly well-tolerated, common adverse effects include gastrointestinal symptoms (nausea, vomiting, diarrhea), neurological symptoms (sedation, ataxia, tremor), weight gain, and alopecia. Less common adverse effects include VPA-induced parkinsonism and cognitive impairment. We describe a patient who developed parkinsonism and cognitive impairment eight years after starting divalproex sodium for bipolar disorder, type I. Over time, the patient's parkinsonian symptoms progressed, and the motor symptoms were partially responsive to carbidopa/levodopa. Her mild cognitive impairment was, for the most part, stable on donepezil. Rapid discontinuation of divalproex sodium resolved the parkinsonian symptoms as well as the cognitive impairment. A brief review of the literature regarding VPA-induced parkinsonism and cognitive impairment in adults is included. Given the reversible nature and potential severity of VPA-induced parkinsonism, improved recognition in psychiatric populations is critical, particularly after extended VPA exposure. To the best of our knowledge there are no reports describing the onset of VPA-induced parkinsonism in psychiatric patients more than eight years after starting VPA.

Key Words: valproic acid, parkinsonism, cognitive impairment, bipolar disorder

INTRODUCTION

VPA is an 8-carbon branched-chain carboxylic acid that was first synthesized by B.S. Burton in 1882 (Burton 1882). VPA is used to manage epilepsy, bipolar disorder, PTSD, impulse control disorders, neuropathic pain, and prophylaxis of migraine headaches (Pallanti et al. 2002, Adamou et al. 2007, Bialer and Yagen 2007). VPA carries a few serious black box warnings such as hepatotoxicity, hemorrhagic pancreatitis, and fetal neural tube defects (Kanner and Balabanov 2002). Although not listed as a black box warning, VPA-induced thrombocytopenia can result in platelet dysfunction and bleeding (Nasreddine and Beydoun 2008). Other common side effects include weight gain and increases in serum triglycerides, cholesterol, and fasting glucose (Wirrell 2003, Grosso et al. 2009). Neurological side effects include encephalopathy, exacerbation of epilepsy, and cognitive decline attributed to hyperammonemia (Gerstner et al. 2006, Buechler and Buchhalter 2007, Nicolai et al. 2007, Varoglu 2009). An action-based tremor was initially thought to be the main potential VPA-induced movement side effect; more recent neurology reports detail VPA as a key source of drug-induced parkinsonism (Hyman et al. 1979, Karas et al. 1982, Jamora et al. 2007).

There are a few studies on VPA-induced reversible parkinsonism and dementia, particularly in epilepsy patients. One study found the prevalence of VPA-induced parkinsonism at a tertiary epilepsy center to be as high as 5.04% (Jamora et al. 2007). However, reports on VPA-induced reversible parkinsonism and cognitive decline in the psychiatric population are scarce. It is important to be vigilant about VPA-induced

reversible parkinsonism in psychiatric patients because treatment with dopamine agonists can exacerbate mood or psychotic symptoms.

We present the case of an elderly Caucasian female receiving divalproex sodium (containing VPA) for bipolar disorder, type I, who insidiously developed VPA-induced reversible parkinsonism with cognitive impairment eight years after starting divalproex sodium.

Case Presentation

GB is a 71-year-old Caucasian female with a past psychiatric history of bipolar disorder, type I, generalized anxiety disorder, and a past medical history of obstructive sleep apnea, hypertension, recurrent urinary tracts infections (UTIs), and arthritis. In 2007, eight years after starting divalproex sodium for mood stabilization, GB started to experience falls as well as some mild difficulty with short-term memory. On neurological examination, she did not exhibit any resting, postural, or action tremor. However, bradykinesia, mild cogwheel rigidity, hypomimia, and a reduced arm swing were present on physical examination. For these parkinsonian symptoms, she was started on carbidopa/levodopa with a total daily dose of 300 mg of levodopa. Magnetic resonance imaging (MRI) of the brain at this point did not reveal normal pressure hydrocephalus (NPH), vascular parkinsonism, or other etiologies for her symptoms. Between 2007 and 2010, GB's parkinsonian symptoms remained mostly stable on a total daily dose of 300 mg of levodopa and no dose adjustments were necessary.

In 2010, GB's motor symptoms (bradykinesia, cogwheel rigidity, postural instability) had started to progress. In the medication "on" state, she scored 11 points on the Unified Parkinson's Disease Rating Scale (UPDRS) part III motor score, and the dose of carbidopa/levodopa (25 mg/100 mg) was increased to 1 tablet four times a day (Martinez-Martin et al. 1994). Her medication regimen included divalproex sodium 500 mg during the day and 750 mg at night, venlafaxine extended release (ER) 225 mg daily, and clonazepam 0.25 mg during the day and 0.5 mg at bedtime. VPA level was in the therapeutic range, at 72 mg/L. An MRI in 2010 showed generalized volume loss, enlarged ventricles and a flow void through the aqueduct increasing suspicion for NPH; therefore a lumbar puncture was performed. Opening pressure was 14 mmHg and 30 cc of fluid was drained. There was no noticeable change in her gait after the lumbar puncture. The cerebrospinal fluid (CSF) was colorless and appeared clear. CSF red and white blood counts were within normal limits.

GB's motor function continued to progressively decline. In 2011, she developed a head titubation. On physical exam, there was moderate bradykinesia, cogwheel rigidity, a markedly stooped posture, and a reduced arm swing. In the medication "on" state, her UPDRS part III motor score had

increased to 24 points; carbidopa/levodopa (25 mg/100 mg) was increased to 1 tablet six times daily. The patient also developed auditory hallucinations, suspected to be levodopa-induced, and was prescribed quetiapine 50 mg daily. Her cognition had declined from prior visits: she reported difficulty with short-term memory, processing speed, and attention. On testing, clock drawing, immediate registration, and recall were intact, but the patient could only name 7 animals in 60 seconds, suggestive of dementia (Canning et al. 2004). She was then started on donepezil 5 mg daily. Divalproex sodium was reduced to 500 mg twice a day due to somnolence and falls. Thyroid stimulating hormone, basic metabolic panel, complete blood count, liver function panel, coagulation factors, uric acid, iron levels, vitamin B12, and methylmalonic acid levels were all within normal limits.

The increase in levodopa alleviated most of GB's motor symptoms. In 2012, in the medication "on" state, her UPDRS part III motor score had decreased to 19 points. Her bradykinesia and cogwheel rigidity had improved. The head titubation had disappeared. Her posture was less stooped and arm swing was improved. However, she was experiencing fatigue, so carbidopa/levodopa (25 mg/100 mg) was decreased to 1 tablet three times a day. There was no significant decline in her memory compared to 2011, and on testing, the patient was able to name 9 animals in 60 seconds. VPA level had decreased to 48.0 mg/L; however, her mood symptoms were mostly well-controlled. Head CT in 2012 showed ventricles proportionate in size to cerebral atrophy. A few months later, in the medication "on" state, her UPDRS part III motor score had further decreased to 10 points. Her memory remained stable on donepezil 5 mg daily. Due to her insomnia and mild dysphoria, mirtazapine 15 mg at bedtime was added to the regimen. Although she denied any side effects, the patient discontinued mirtazapine within 3 months.

A few months later, GB reported a re-emergence of parkinsonian symptoms (hypomimia, soft voice, tremor of the face and jaw, rigidity in the right and left upper extremities, bradykinesia, and postural instability). In the medication "on" state, her UPDRS part III motor score had increased to 14 points. Her cognition remained mostly stable. VPA level had decreased further to 42.0 mg/L. The possibility of VPA-induced parkinsonism was raised and divalproex sodium was rapidly tapered over 9 days. Carbidopa/levodopa was tapered down over a month. Two months after discontinuing divalproex sodium, GB's parkinsonian symptoms had mostly resolved, and her UPDRS part III motor score decreased to 6 points. On examination, there was no tremor, no stiffness or slowness, and no postural instability. Her cogwheel rigidity had improved, her voice was less tremulous, and her gait was less stooped. Since the discontinuation of divalproex sodium and carbidopa/levodopa, there has not been a re-emergence in parkinsonian symptoms or hallucinations. A few months

after discontinuing divalproex sodium, there was a gradual improvement in the patient's memory and she scored a 28/30 on the Mini-Mental State Exam. Subsequently, donepezil was discontinued. For 12 months after the discontinuation of divalproex sodium, there was no re-emergence of any parkinsonian or dementia symptoms. The patient has remained stable on clozapine 225 mg daily, clonazepam 0.25 mg during the day and 0.5 mg at bedtime, and venlafaxine ER 225 mg daily.

The Naranjo algorithm was used to assess the likelihood that the parkinsonism was the result of an adverse reaction to VPA (Naranjo et al. 1981). The calculated Naranjo score for the patient was a 6, indicating that VPA probably induced the parkinsonian symptoms.

DISCUSSION

Eight years after divalproex sodium was initiated for management of bipolar disorder, type I, the patient described had a reversible parkinsonian syndrome and cognitive impairment, which resolved after discontinuation of divalproex sodium. Other etiologies for reversible parkinsonism were considered. Anti-depressants have been associated with extrapyramidal symptoms (EPS) and selective serotonin-reuptake inhibitor-induced parkinsonism, which is thought to be caused by serotonin's inhibitory action on extrapyramidal dopamine (Caley 1997). It is unlikely, however, that venlafaxine was the primary cause of the motor symptoms, because withdrawal of divalproex sodium improved the parkinsonian symptoms. Divalproex sodium can increase quetiapine levels by as much as 77% through cytochrome P450 2D6 inhibition, and an increase in quetiapine could result in dose-dependent EPS; however, quetiapine has a lower incidence of EPS and the patient took this medicine for a relatively short period (Cheer and Wagstaff 2004, Aichhorn et al. 2006). The symptoms were not secondary to NPH, since draining fluid via a lumbar puncture did not improve the motor or cognitive symptoms; also, imaging data acquired for the purpose of exploring this etiology were mixed (Wikkelso et al. 1982, Morishita et al. 2010). The mild generalized cerebral volume loss seen on imaging could be secondary to pseudoatrophy of the brain that is reversible upon discontinuation of divalproex sodium; however, no follow up head imaging was performed (Armon et al. 1996). Furthermore, the absence of urinary incontinence, the presence of other motor symptoms, and partial positive response to levodopa were more suggestive of parkinsonism (Hakim and Adams 1965, Morishita et al. 2010).

Although discontinuation of divalproex sodium may uncover an underlying Parkinson's disease, it does not appear to have done so in this patient because of the paucity of parkinsonian symptoms a year after discontinuing divalproex sodium. However, it is always possible that idiopathic Parkinson's disease could become apparent in the future. Further

consideration in differentiating idiopathic Parkinson's disease from VPA-induced parkinsonism could include the use of the DaTSCAN scan (Ioflupane (^{123}I)), which was FDA approved in 2011(Brigo et al. 2014). Ioflupane binds to presynaptic dopamine receptors particularly in the striatal region (Antonini et al. 2003). The DaTSCAN is not used to confirm the diagnosis of idiopathic Parkinson's disease but might differentiate between idiopathic Parkinson's disease and secondary parkinsonian conditions (Brigo et al. 2014). A meta-analysis found that the DaTSCAN had sensitivity and specificity values above 85% and 80%, respectively, in differentiating between idiopathic Parkinson's disease and vascular or drug-induced parkinsonism; however, no definitive conclusions were made (Brigo et al. 2014). Clinical judgment may also help to differentiate VPA-induced parkinsonism from idiopathic Parkinson's disease; however, VPA-induced parkinsonism presents with characteristics of both drug-induced parkinsonism (DIP) and idiopathic Parkinson's disease (Silver and Factor 2013). Typically, DIP presents with a sub-acute onset, whereas VPA-induced parkinsonism may appear many years after VPA is initiated (Bohlega and Al-Foghom 2013). Freezing occurs rarely in both DIP and VPA-induced parkinsonism (Bohlega and Al-Foghom 2013). Furthermore, DIP is characterized by symmetric rigidity, poor response to levodopa agents, and a prominent resting tremor (Bohlega and Al-Foghom 2013). Demographically, DIP tends to occur in older females (Bohlega and Al-Foghom 2013). VPA-induced parkinsonism occurs in both males and females (Masmoudi et al. 2006). It is unclear if there is a positive relationship between the dose of VPA and the severity of parkinsonian symptoms, although a dose reduction does improve the symptoms (Masmoudi et al. 2006, Silver and Factor 2013). Risk factors associated with DIP include neuroleptic use, increasing age, genetic predisposition, and HIV infection (Metzer et al. 1989, Avorn et al. 1995, Mirsattari et al. 1998, Uchida et al. 2009). Protective factors for DIP include anti-cholinergic drugs and smoking (Rodriguez-Navarro et al. 2007).

An electronic search of all published articles on VPA-induced parkinsonism and cognitive impairment in adults was performed on PubMed, Google Scholar, MEDLINE, and EMBASE up until August 2014. Our literature review found 34 case reports, only 6 with primary psychiatric diagnoses, and two epilepsy case series (Lautin et al. 1979, Wils and GolÜKe-Willemse 1997, Onofrj et al. 1998, Iijima 2002, Easterford et al. 2004, Ricard et al. 2005, Gaubert et al. 2006, Masmoudi et al. 2006, Ristic et al. 2006, Salazar et al. 2008, Khwaja GA et al. 2010, Sleegers et al. 2010, Evans et al. 2011, Frevert 2011, Silver and Factor 2013). In these 34 case reports, the mean age was 62.71 years+/- 12.32 years, the mean total daily dose of VPA was 1183.82 mg +/- 425.28 mg, the time to onset of parkinsonian symptoms after starting VPA ranged from 4 days to 25 years, VPA blood levels

Table 1. Case reports on VPA-induced reversible parkinsonism and cognitive impairment in psychiatric patients.

Case	Age (years)	Gender	Diagnosis	Total daily Dose of VPA (mg)	VPA blood levels (mg/L)	Time to onset of symptoms after starting VPA	Cognitive Impairment	Time to improvement or resolution of symptoms after stopping VPA
1 (Wils and GolÜKe-Willemse 1997)	70	F	Bipolar Disorder	750	48-52	10 days	N/A	N/A
2 (Silver and Factor 2013)	44	F	Depression	250	N/A	2.5 years	Yes	2 years
3 (Silver and Factor 2013)	72	F	Depression	1000	N/A	1.5 years	Yes	3 days
4 (Silver and Factor 2013)	74	M	Bipolar depression	1500	N/A	3 years	No	4 months
5 (Ricard et al. 2005)	58	M	Bipolar Disorder	1000	79	7 months	Yes	1 year
6 (Lautin et al. 1979)	52	M	Schizophrenia	1000	N/A	4 days	N/A	2 days

ranged from 11mg/L to 112 mg/L, and the time to improvement or resolution of parkinsonian symptoms after stopping VPA ranged from 2 days to 20 months. 19 of these cases were female. Jamora and colleagues found that 5.04% of epilepsy patients referred to an epilepsy tertiary referral center had VPA-induced parkinsonism (Jamora et al. 2007). The mean dose of VPA prescribed was 750 mg per day. Reduction of VPA improved parkinsonian symptoms (Jamora et al. 2007). Armon and colleagues examined 36 patients in an epilepsy clinic with parkinsonism and cognitive impairment who were on VPA for greater than 12 months (Armon et al. 1996). Within 3 months of discontinuing VPA, 96% of the patients had a significant improvement in their parkinsonian symptoms (Armon et al. 1996). The epilepsy case series data suggest that VPA-induced parkinsonism is under-reported and under-recognized in psychiatric populations. Of the six case reports of VPA-induced parkinsonism in patients with primary psychiatric diagnoses, three patients had bipolar disorder (see table I). In all six cases, the onset of parkinsonian symptoms occurred within 3 years after initiating VPA; the total daily dose of VPA ranged from 250 mg to 1500 mg. Furthermore, there was a high variability in time to resolution of symptoms after discontinuing VPA. At least half of these 6 cases were associated with cognitive impairment, which improved after discontinuing VPA (see table I) (Lautin et al. 1979, Wils and GolÜKe-Willemse 1997, Ricard et al. 2005, Silver and Factor 2013).

CONCLUSION

We present the case of a female with bipolar disorder who progressively developed VPA-induced reversible parkinsonism and cognitive impairment eight years after starting divalproex sodium. Her motor symptoms progressed from mild to severe.

Due to the onset of symptoms many years after starting divalproex sodium, the temporal relationship was not immediately apparent. Discontinuation of divalproex sodium resolved both the motor and cognitive symptoms. Data on VPA-induced parkinsonism in the psychiatric population is lacking, despite the frequent long-term use of VPA to treat psychiatric disorders. Given the neuropsychiatric side effects of levodopa and other dopaminergic agents which may be used to treat parkinsonism, and the reversible nature and potential severity of VPA-induced parkinsonism, improved recognition in psychiatric populations, particularly after extended VPA exposure, is critical. Larger studies of VPA-induced parkinsonism and cognitive decline in psychiatric disorders are needed.

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